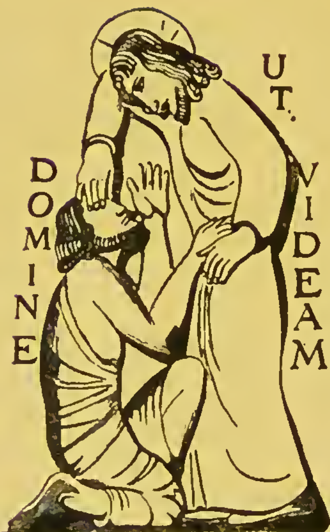
Hunterian Lectures, 1905

MAYOU

Presented
To The Royal ~~Westminster~~ London Ophthalmic Hospital.
by Mary R. Wilson
Cornell University
N.Y.



The Changes Produced by Inflammation in the Conjunctiva

(HUNTERIAN LECTURES, R.C.S., 1905)

BY

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TO

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TEACHER OF OPERATIVE SURGERY, AND SURGEON TO

KING'S COLLEGE HOSPITAL, ETC.,

MY TEACHER AND FRIEND.

PREFACE.

The chief object of this book is to record the results of over three years' work on a subject which is perhaps one of the most difficult and at the same time one of the most important in Pathology, namely, inflammation.

Whilst admitting from the beginning that the explanation of the changes found in the tissue is surrounded by many difficulties and pitfalls, I have attempted to put forward some views of the subject which may suggest a basis for further researches, derived from the study of the conjunctiva, a tissue which lends itself to accurate investigation, both clinical and pathological.

I have not attempted to treat of the whole subject, but rather to describe the conditions which I have personally investigated. The work of other authors which I have not personally verified I have referred to in the text. I may add that this book contains part of the work which obtained the Jacksonian Prize (1903); the original sections (some 300), together with the original drawings (some 150), can be examined at the Royal College of Surgeons.

My best thanks are due to Mr. W. I. Hancock, F.R.C.S., for his help in revising the proof sheets.

M. S. MAYOU.

WEYMOUTH STREET,
PORTLAND PLACE,
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CONTENTS.

LECTURE I.

LECTURE II.

LECTURE III.

THE

Changes Produced by Inflammation in the Conjunctiva.

LECTURE I.

INTRODUCTION.

For the proper understanding of the disease of an organ it is essential to know the developmental origin, and the macroscopic and microscopic anatomy of the organ affected. I therefore propose to begin these lectures with a short account of some special observations on the developmental and morphological origin of the conjunctiva, laying especial stress on the conditions at birth and the changes which occur during the first few weeks of life, these having very important bearings on the study of the formation of the lymphoid tissue and of the changes produced by chronic inflammation. I shall next describe the histological changes which take place in the various inflammatory diseases which I have had the opportunity of investigating. In studying these changes, amongst other stains, I have used Pappenheim's plasma stain, which,

so far as I know, has not previously been employed for demonstrating the changes occurring in the cells of the conjunctiva. It gives results far superior to those obtained by Unna's polychrome methylene blue stain, which stain it has largely superseded for demonstrating the protoplasm of the cells elsewhere in the body.

Method of using Pappenheim's Plasma Stain :—

Fix the tissue in alcohol or perchloride of mercury.
Embed in paraffin.
Cut sections and fix on slide.
Dissolve out paraffin with xylol.
Remove xylol with absolute alcohol.
Stain.

Pappenheim's Formula :—

"Two knife points of methyl green.
"Four knife points of pyronine.
"Distilled water—half a large test tube.
"Mix and filter.
"Test the stain by dropping on to filter paper."
Good rings of individual colour should be produced.
The stain does not keep in good condition for more than two weeks and should be tested each time before use.
"Stain sections for five minutes and differentiate with resorcin—three knife points.
"Absolute alcohol—half a test tube."
Dehydrate rapidly in absolute alcohol.
Clear in xylol.
Mount in balsam.

The study of these inflammatory changes throws some light on the origin of the mononuclear leucocytes and plasma cells and the changes which these cells undergo in inflammatory affections. A. Whitfield,[1] as the result of many years'

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[1] Whitfield, A., *Journal of Dermatology*, January, 1904.

experimental and histological investigations, has come to the conclusion that the endothelial and perithelial cells play the most important part in the production of mononuclear leucocytes and plasma cells. I have come to a somewhat similar conclusion with regard to the conjunctiva; the changes which occur here afford one of the strongest arguments in favour of this theory.

Previous to this there were two main theories with regard to the origin of the plasma cells; either (1) that they were derived from the fixed connective tissue cell (Unna), or (2) from the mononuclear leucocytes; most English and Continental pathologists agree with this latter view. I shall endeavour to point out the importance of these cells as indicating by their degeneration the active site of a disease, and also to show their distribution in the various forms of inflammation of the conjunctiva.

Further, I shall endeavour to show the significance of follicular formations in the conjunctiva.

In connection with trachoma I shall show the results of treatment by the X-rays, which method of treatment I introduced. In primary and secondary xerosis I shall point out the changes in the epithelium and the influence of surface tension in the production of the plaques. Several other minor points will be treated of.

My best thanks are due to Dr. Whitfield and

Mr. E. Treacher Collins for the help they have given me in the preparation of these lectures, and Mr. Roxburgh for much of the pathological material.

Development.

At the time the conjunctiva shows signs of differentiation from the surrounding epiblast the facial cleft is not entirely closed, it being still open in the region of the lachrymal sac. The eyes are situated laterally in the head, and have not yet moved down to occupy their permanent position. In most of the lower vertebrata this lateral position of the eyes is a permanent one, and it is only when the higher types are reached, such as the ape, that the eyes take the more anterior position associated with binocular vision.

The conjunctiva is derived from the surface epiblast covering the fœtus, the first indication of its differentiation from that structure taking place about the eighth week of human fœtal life; the primary and secondary optic vesicles are well formed by that time, but the lens is not entirely separated from the embryonic cornea by the ingrowth of the iris. The sclera is just showing signs of differentiation from the surrounding mesoblast. A groove, surmounted by a fold, appears above and below the cornea, uniting first at the outer side and finally at the inner, where it becomes thrown into a thick vertical fold which

subsequently forms the plica semilunaris (membrana nictitans of birds), which appears about the ninth week of fœtal life. At the limbus on the inner side a marked fold is found projecting forwards, which after birth becomes flattened out. In

FIG. 1.—Human fœtus, 10 weeks, 4½ cm. long, showing the folding of the epithelium at the eyelid margins as union takes place between the upper and lower lid. A, Upper lid ; B, lower lid with the surface epiblast slightly torn on the surface ; C, cornea ; D, conjunctival sac ; E, union between the eyelids.

Note.—The conjunctival and epidermal epithelium are both covered by a single layer of cells, whilst that between the margins of the lids is thickened and thrown into folds.

vertical section the eyelid sulcus is seen to be produced by a direct folding of the surface epiblast, the ridges forming the first indication of the developing eyelid. In some forms of fish development is arrested at this stage.

The two rudimentary eyelids thus formed grow rapidly forwards in contact with the globe, and just before union takes place are thrown into a number of horizontal folds at their margin (fig. 1).

Directly the margins of the eyelids have come in contact with each other, which takes place at

FIG. 2.—Human fœtus, fourth month, 11 cm. A, union of eyelids; B, conjunctival surface; C, hair follicles and Meibomian glands causing separation of the anterior part of the union.

Note the curve produced by the turning forwards of the hair by the opposing lid.

the tenth week of fœtal life ($4\frac{1}{2}$ cm. length), there is a proliferation of epithelium between the two surfaces out of all proportion to that in either the skin or the conjunctival surface; and they become firmly united together and at the same

time tightly stretched over the globe, which seems to assist materially in their development, since in severe degrees of microphthalmos the eyelids are short and the conjunctival sac ill developed.[1] If failure or incomplete union of the lids should take place from interposition of the amnion or other cause, there would result a condition varying in degree from a mild congenital lagophthalmos (in which condition the upper lid, because development after union takes place principally at its own expense, fails to cover the globe) up to a complete absence of the lids with the formation of a skin-like conjunctiva. At this time the conjunctiva is a closed sac lined by a single layer of epiblast, and although the surface epiblast then begins to thicken, that lining the conjunctival sac remains as a single layer until after the lids have separated—a fact which I do not think has been previously pointed out.

To see if this rule were a general one throughout the animal kingdom, I have examined the following animals in the fœtal state: cat, rat, rabbit and snake, and find it to hold good in all I have examined; the last reptile shows so many points of interest in the arrangement of its conjunctiva that I shall, before going on, give a short account of it together with its development.

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[1] Mayou, M. S., "On Microphthalmos," *Trans. Ophth. Soc.*, vol. xxiv., p. 346.

Arrangement and Development of the Conjunctiva in Snakes.

The snakes were obtained from the Zoological Gardens, Regent's Park, by the courtesy of the Curator, Mr. Beddard.

The following specimens were obtained :—

(1) Yellow Cobra (*Naia flava*), South Africa.

(2) American Grass Snake (*Contia vernalis*), North America.

(3) Long-nosed Viper (*Vipera ammodytes*), South Europe.

(4) Four-lined Snake (*Coluber quatuor lineatus*), Europe.

(5) Dark-green Snake (*Zamenis Gemonensis*), Europe.

(6) American Glass Snake (*Ophiosaurus ventralis*), North America.

(7) Sharp-nosed Snake (*Lioheterodon madagascariensis*), Madagascar.

(8) Indian River Snake (*Tropidonotus piscator*), India.

(9) Common Viper (*Vipera berus*), British Islands.

The facility of obtaining the common Grass Snake led me to use this reptile exclusively in studying the development.

The snake when casting its skin becomes blind, owing to a layer of keratin on the surface of the eyes becoming opaque before being shed. This layer is not derived from the surface of the cornea,

but from what I hope to be able to show is a membrana nictitans which divides the conjunctival sac into two portions. If the several varieties be examined, it will be seen that the eyelids differ considerably in the extent to which they cover the globe ; thus, in the Common Viper the lids almost meet over its surface, whilst in the American Grass Snake there is only a groove (figs. 3 and 4).

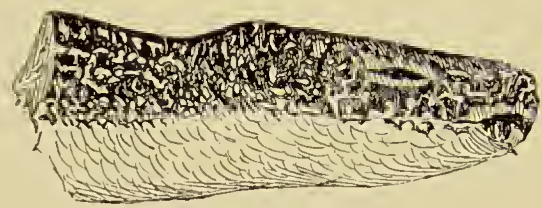


FIG. 3.—Head of the *Vipera Berus.*
Note the almost complete development of the eyelids.

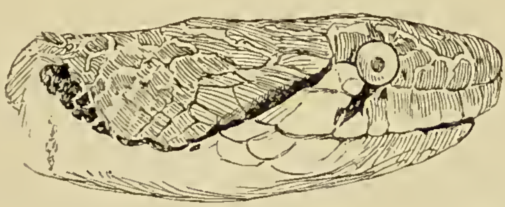


FIG. 4.—Head of the *Coluber Quatuor Lineatus.*
Note ill-developed eyelids and transparent membrane nictitans.

If a vertical section be made through the eye and eyelids the conjunctival sac is seen to be divided into two portions : an outer, lined with epithelium and covered by a thick layer of keratin, and an inner closed sac, lined by a single layer of epithelial cells ; these cells are flattened in the region of the cornea, but become cuboidal in the fornices. The

cells are of the embryonic type; this is a point I wish to bring out, as I shall refer to it again when coming to the human conjunctiva (figs. 5 and 6).

Stretching from one lid to the other is a membrane, which is covered externally by a double

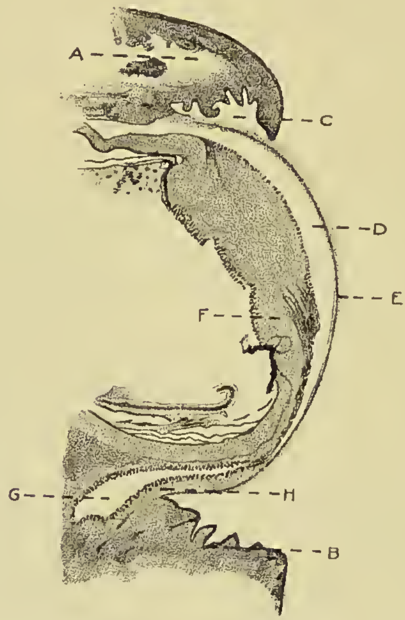


FIG. 5.—Snake's Head. Vertical section through the eye and Eyelids of the *Zamenis gemonensis*. A, Upper lid; B, lower lid; C, outer conjunctival sac; D, inner conjunctival sac; E, third eyelid; F, cornea; G, fornix; H, point at which the mesoblast of the third lid becomes continuous with the mesoblast of the lower lid.

layer of epithelial cells and a thick layer of keratin like the covering of the external sac, and internally by a single layer of epithelial cells like the inner sac; between these is a layer of mesoblast, continuous with the mesoblast of the eyelids.

A common Grass Snake's egg takes about sixty days to hatch. The eggs procured were said to have been laid on July 10. On July 12 they were put into an incubator at a temperature of 30° C. An egg opened on July 16 showed a well-marked primitive streak. On July 18 the

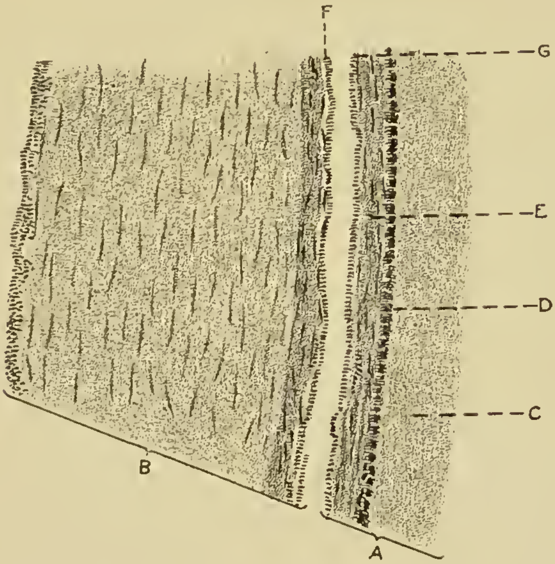


FIG. 6.—Portion of the cornea and third lid (high power). A, Third lid ; B, cornea ; C, surface keratin ; D., layer of epithelial cells ; E, mesoblast of the third lid : F, G, single layer of epithelial cells lining the inner conjunctival sac.

primary and secondary optic vesicles were well formed ; the cornea was present in contact with the amnion, the retinal and hæmoglobin pigments being the only ones present in the body ; there was a small notch external to the cornea showing the commencement of the rudimentary eyelids. (Length of fœtus in membranes 8 mm.)

On July 20 a somewhat curved, horse-shoe-shaped membrane with a whitish margin could be seen growing across the surface of the cornea from the inner and anterior end of the palpebral fissure. (Length of fœtus in membranes 11 mm.) (fig. 7).

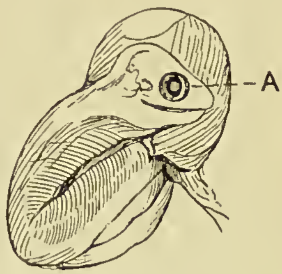


FIG. 7.—Surface view of the fœtal snake tenth day of incubation, showing the third eyelid (A) opaque at its margin growing across the globe.

FIG. 8.—Horizontal section of a snake's eye, ninth day of incubation, showing membrana nictitans (A) growing from the inner side.

Vertical section of the posterior or outer portion of the palpebral fissure showed the lids above and below, but no membrana nictitans, whilst horizontal section showed the growth of the membrana nictitans from the inner side across the globe

(fig. 8). This membrane during fœtal life, as it grows across the cornea, is opaque at its margin and semilunar in shape. Its blood supply is derived from two vessels which arise on the inner side and run round its margins, anastomosing with

FIG. 9.—Eyelid union of a cat three days after birth. A, Upper lid : B, lower lid ; C, cornea covered by a single layer of epithelium ; D, union of eyelids.

Note.—Separation has taken place anteriorly and posteriorly by the degeneration of the cells, the middle portion being the last to yield.

each other at the outer side and sending branches inwards towards the centre of the lid ; these vessels disappear after birth. The membrane is transparent until shortly before birth, when it becomes somewhat cloudy, probably through desquamation from the surface, similar to that occurring when the snake casts its skin. Thus it will be seen

that the conjunctival sac of the snake is divided into two by a persistent membrana nictitans, and that the inner sac is lined by a single layer of epithelium of an embryonic type, which persists as such throughout life.

The cat and rabbit both show extremely well the process of separation of the eyelids, which in these animals does not occur till after birth and is therefore easily studied, the epithelium lining their conjunctival sac remaining as a single layer until after separation has taken place (fig. 9).

The Manner and Date of Separation of the Eyelids in the Human Fœtus.

In looking up the literature of this subject I was at once struck by the number of different dates given by various authors for the separation of the lids, varying from the seventh month till shortly before birth. When we remember that a certain number of living children are born at the seventh month, and reflect that these children are not born with closed eyelids like the cat or dog, we realise that there must be a fallacy somewhere.

The age and length of the fœtuses examined were as follows :—

Length.	Approximate Age.	Condition of Lids.
24 cm.	... Fifth month	... Lids separated.
21½ ,,	... ,, ,,	... ,, ,,
20 ,,	... ,, ,,	... ,, ,,
11 ,,	... Fourth month	... Lids joined, separation commencing anteriorly, growing out of eyelashes.

Length.		Approximate Age.		Condition of Lids.
9 cm.	...	Fourth month	...	Lids joined, separation commencing anteriorly, growing out of eyelashes.
7 ,,	...	Third month	...	Firmly united.
4½ ,,	...	Thirteenth week	...	Primary union just taking place.

The above fœtuses were examined both macro- and microscopically. The description of the condition of the lids and conjunctiva in the ten weeks' fœtus (4½ cm.) I have already given. A fœtus of the third month (7 cm.) showed the eyelids firmly united together by epithelium, with down growth of the epithelium from the junction of the lids commencing to form the Meibomian glands and hair follicles, the former appearing rather before the latter.

During the early part of the fourth month (fœtus 9 and 11 cm.), the eyelashes grow out from between the closed lids and materially assist in the separation of the anterior portion of the union, which is the first to yield, the uniformity of the curve of the lashes being produced by the impinging of the growing lash on the opposing eyelid (fig. 2).

I think that cases of congenital trichiasis (Stephenson, *Trans. Oph. Soc.*, vol. xiv.) may be accounted for by irregularity or mal-union of the lids allowing the lashes to grow out straight without impinging on the opposite eyelid, and so altering the direction of the follicle as to produce non-uniformity of the curve. After separation of the anterior part

of the junction of the lids there is a degeneration of the epithelial cells of the posterior part of the union, better seen in the cat about the third day after birth than in the human embryo (fig. 9). Final separation takes place by degeneration of the epithelium in the mesial portion of the junction, which is therefore the last to yield.

It has already been seen in the snake that the portion of the conjunctival sac which is permanently closed is lined by a single layer of epithelium of embryonic character. In the cat (third day after birth) the epithelium over the surface of the bulbar conjunctiva remains as a single layer until separation of the lids has taken place (ninth day), so I think it may be taken that thickening of the bulbar conjunctiva is positive evidence of separation having taken place. This thickening of the conjunctival epithelium I found took place in fœtuses over 20 cm., viz., at the beginning of the fifth month (fig. 10), the thickening taking place first, and spreading from the epithelial bond of union between the eyelids. Another argument in favour of the thickening of the epithelium being due to the separation of the lids is the fact that when the lids have failed to unite, as occurs in cases of clefts of the lids, or in cases where the lids are completely absent (cryptophthalmos), the epithelium is very much thickened, so much so that it resembles skin. Thus, I think, the

comparative frequency of the so-called dermoid patches of the conjunctiva so often associated with deformity of the eyelids is explained.

Further evidence that the lids have partially separated at the fifth month is found in the

FIG. 10.—Human fœtus, 20 cm. Fifth month (eyelids separated). A, Superior fornix of the conjunctiva showing commencing thickening of the epithelium.

fact that the Meibomian glands are actively secreting at that date, and it is possible to squeeze secretion from them; microscopically this secretion is made up of fatty material with a quantity of epithelial cells.

Description of the Conjunctiva at Birth.

The following observations were based on the examination of three healthy fœtuses at full term, in a good state of preservation. They were hardened in formol, two of them being cut in celloidin and one in paraffin.

FIG. 11.—Epithelium of the tarsal conjunctiva near the lid margin at birth. A, surface layer; B, basal layer. Camera lucida $\frac{1}{12}$ oil. No. 8 eyepiece.

When the child is born the eyelids are tightly closed, the skin being thrown into numerous wrinkles and covered with a fatty material. The margins of the lids are usually in contact with each other, but occasionally the upper lid is found overlapping the lower.

In the child at birth, as compared with the adult, the length of the palpebral aperture is

small in comparison with the size of the conjunctival sac. The lining membrane is thrown into numerous folds in the fornices and over the surface of the globe. The margins of the lids are covered with fatty secretion from the Meibomian glands, and with epithelial *débris.*

The Epithelium.—Over the lower part of the tarsus this is much thicker than it is in the adult conjunctiva, owing, no doubt, to its close proximity to the margins of the lids, in which

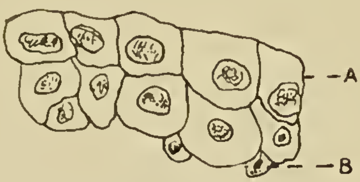


FIG. 12.—Epithelium of the anterior fold of the fornix at birth. A, Surface layer; B, basal layer. Camera lucida $\frac{1}{12}$ oil. No. 8 eyepiece.

Note the thickness of the epithelium of the tarsal conjunctiva, the absence of any flattened layer on the surface and the more cuboidal shape of the cells.

thickening first begins. It is here some five cells in thickness, and it is the only situation in which it is thicker than in the adult, and, like the rest of the epithelium of the conjunctiva, there is an absence of any flattened epithelial cells on the surface, the cells being cuboidal in shape (fig. 11). On the anterior part of the retrotarsal fold the epithelium is only from two to three cells in thickness, being much thinner than the adult epithelium in that region (fig. 12).

That of the bulbar conjunctiva is, again, not so thick as that of the adult, but next to the epithelium covering the tarsus it is the thickest part of the epithelium of the conjunctiva at birth (fig. 13). In the fornices at the bottom of the folds the cells show signs of mucoid change to such an extent that in the three cases examined the basement membrane was completely bare in places and would have allowed a ready entrance of organisms to the subconjunctival tissues (fig. 14).

FIG. 13.—Epithelium of the bulbar conjunctiva at birth. A, Surface layer; B, basal layer. Camera lucida $\frac{1}{12}$ oil. No. 8 eyepiece.

The corneal epithelium is about three cells in thickness, but to compensate for this there is a great thickening of the substantia propria, both in comparison to the thickness of the sclera and to that of the adult cornea (fig. 15).

The subconjunctival tissue in the region of the bulb contains a quantity of elastic fibres, which are finer than those in the adult conjunctiva. There does not seem to be any

elastic tissue in the subepithelial conjunctival tissue covering the tarsus.

In the fornices the subconjunctival tissue is very loose and rich in blood-vessels and lymphatic

FIG. 14.—One of the folds from the bulbar conjunctiva of a new-born child showing the loss of epithelium due to mucoid change in the cells at the bottom of the folds. A, Crypt; B, a point at which the epithelium is almost absent; C, subepithelial tissue.

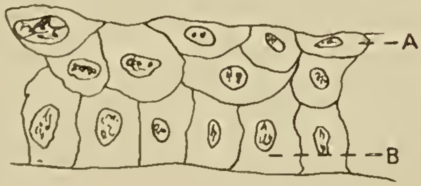


FIG. 15.—Epithelium of the cornea at birth. A, Surface layer; B, basal layer. Camera lucida $\frac{1}{12}$ oil. No. 8 eyepiece.

spaces, but there is a complete absence of leucocytes, which do not appear until after birth, when the fornices become filled with

mononuclear leucocytes and a few plasma cells, which spread later to the subconjunctival tissue covering the tarsus. In other lymphoid tissue, such as the tonsil, mononuclear leucocytes are present for several weeks before birth, and are evidently produced from the cells of those structures. In the conjunctiva, therefore, the lymphoid tissue is the result of irritation and is

FIG. 16.—Polypus originating from a fold at the inner end of the conjunctiva of the superior fornix.

of new formation. This will be discussed in more detail when dealing with the histological changes in inflammatory affections of the subconjunctival tissue.

The Œtiology of so-called Supernumerary Caruncle.—There is a small point in the anatomy of the fornix to which I wish to draw attention. At the extreme end of the upper fornix the loose lymphoid tissue ends in a triangular fold which can only be demonstrated by dividing the eyelids and turning them back; it is seen to be connected with the main fornix by a very narrow

band. This is not an uncommon situation for polypoid tumour, which in the case I have examined consisted of lymphoid tissue covered by epithelium (fig. 16). Several of these tumours have been described under different nomenclature, such as supernumerary caruncle; they arise from this triangular piece of lymphoid tissue becoming œdematous and then being nipped between the globe and the eyelid. In examining a number of stillborn children I found one in which during a difficult labour hæmorrhage had taken place into this small mass of loose tissue, with the formation of a red polypoid mass which protruded from between the eyelids. On section it simply consisted of a mass of blood clot covered by epithelium

The glands opening on to the surface of the conjunctiva, with the exception of the mucous glands, seem to be inactive. The secretion of tears from the lachrymal gland does not take place until some time after birth. There are no glands of Henlé present at the time of birth, these being formed subsequently as the result of irritation.

The Changes in the Conjunctiva as the Result of Inflammation.

The general clinical changes produced by inflammation are the same as those found elsewhere in the body, namely, heat, pain, redness, swelling

and loss of function; the special changes I shall describe under their various headings. I will therefore go on to the histological changes resulting therefrom.

The Epithelium.—The changes in the epithelium depend on whether it is kept moist by the lachrymal secretion or whether it is allowed to become dry. If moist, the cells proliferate and undergo greatly increased mucoid changes, being cast off in large numbers in the discharge. The exudation into the subconjunctival tissue causes the surface epithelium to be thrown into folds between papillary formations, so that two epithelial surfaces lie in contact with each other, and it is the cells of these surfaces which show the most extensive mucoid change, commencing at the bottom of the folds, causing some irregularity of the basement membrane, and giving the appearance of a new gland formation (figs. 17 and 18). The glands of Henlé are of this type, the regularity of their formation along the upper margin of the tarsus being due to this being the situation in which the fixed palpebral conjunctiva joins the loose conjunctiva of the fornix; hence folding is more liable to take place. A large gland of this type is often seen at the inner end of the tarsus and is one which most frequently becomes cystic.

Although this is perhaps the most common way in which the so-called glands of the conjunctiva are formed, there may be observed near the

FIGS. 17 and 18.—Polypus of the plica semilunaris. Two of a series of sections showing the process of new gland-formation by simple folding.

Fig. 17.—A, Epithelium undergoing mucoid change; B, sub-epithelial tissue; C, fold of the conjunctiva showing mucoid change at the bottom of the fold, with irregularity of the basement membrane.

Fig. 18.—The fold completed, forming the new gland (D). (Stain: Logwood and Van Gieson.) $\frac{2}{3}$ obj. No. 4 eyepiece.

junction of the moist and dry epithelium a somewhat different modification, which occurs in conditions due to exposure and to chronic inflammation, such as ectropion, secondary xerosis and papillomata of the conjunctiva which have been exposed in the palpebral fissure. As the result of this exposure the epithelium becomes thickened and dips down into the subepithelial tissue in the form

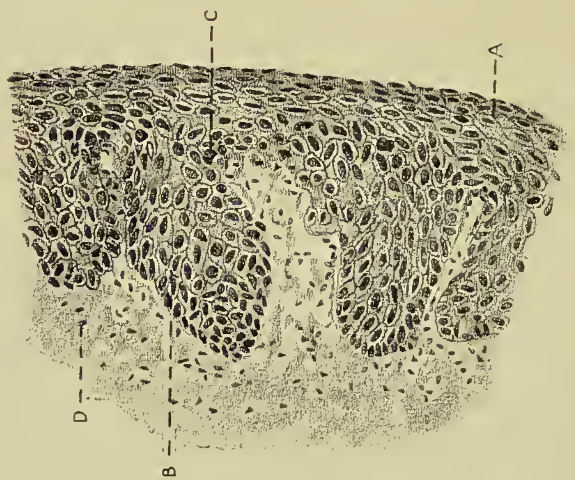


FIG. 19.—Epithelium from a case of ectropion, showing the changes due to exposure. A, Surface epithelium ; B, downgrowth of epithelium ; C,. leucocytes between the epithelial cells ; D, leucocytes in the subepithelial tissue. (Stains : Logwood and Van Gieson.) $\frac{1}{6}$ obj. No. 4 eyepiece.

of papillæ (fig. 19). Mucoid degeneration of the epithelial cells in the centre of these papillæ takes place, with the formation of a flask-shaped mucous gland (figs. 20 and 21). The openings of these new mucous glands are often occluded with epithelial *débris*, with the result that the lower

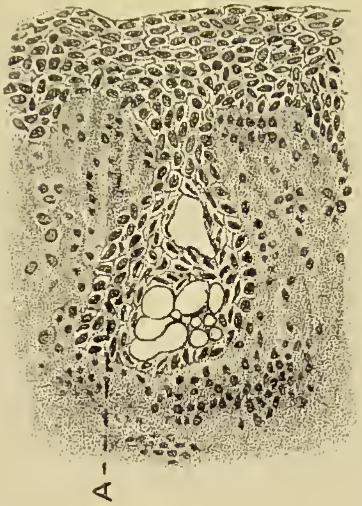


FIG. 20.—New gland-formation. Commencing mucoid change; portion of the epithelium from a case of ectropion from near the junction of the moist and dry surface; A, epithelial downgrowth with commencing mucoid change.

FIG. 21.—New gland-formation. B, Mucoid change completed. Section taken from a polypus of the plica semilunaris. (Stains: Methylene blue and eosin.) $\frac{1}{6}$ obj. No. 2 eyepiece.

end becomes distended to form a cyst. These cysts on the palpebral conjunctiva are extremely common, and one conjunctiva may contain many thousands of them. They are lined by more or

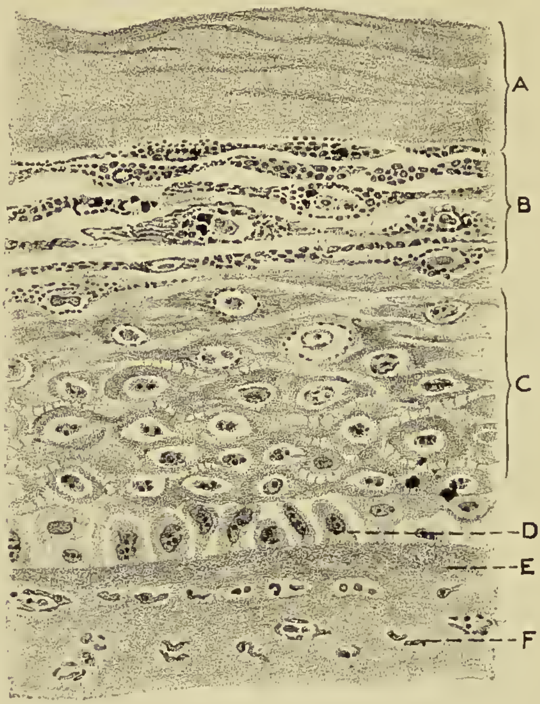


FIG. 22.—Secondary xerosis, following trachoma, from a case in which the whole lower conjunctival sac was covered with a pseudo membrane. A, Layer of keratin on the surface, with adherent Meibomian secretion forming the pseudo membrane ; B, layer showing keratohyalin granules ; C, layer showing intercellular bridges ; D, basal layer ; E, thickened basement membrane ; F, subepithelial tissue.

less flattened epithelium three or four cells deep, and contain epithelial *débris*, which is sometimes calcified. In acute inflammatory conditions of the conjunctiva these cysts, if present, often become

filled with pus, appearing as brilliant yellow points, which, no doubt, subsequently rupture. On the bulbar conjunctiva they are comparatively rare, but when they occur they are usually single and appear as transparent cysts containing clear fluid; they are lined by epithelium having many tuft-like processes, the cells of which are undergoing mucoid change, and supply the fluid for the interior of the cyst (see pl. v., fig. 4).

If the epithelium be dry, as in cases of ectropion, the cells proliferating still remain attached to the underlying epithelium and undergo a process of keratinisation, with the formation of keratin, keratohyalin and prickle cells. The basement membrane becomes irregular, and processes of epithelium dip down into the subconjunctival tissue, forming papillæ. In fact, the epithelium of the conjunctiva which is exposed resembles very closely in structure the true skin, with the exception of the absence of glands, hair follicles, &c. (fig. 22).

Of great interest is the fact that when again moistened, as after ectropion operations, the epithelium goes back to macroscopically resemble its former state, in consequence of the softening of the superficial layers, with subsequent mucoid change in the deeper layers. From this it seems that the presence of lachrymal fluid is necessary to the formation of mucin by the epithelial cells. As the condition known as xerosis is due to this drying of the epithelium it will be described here.

Xerosis of the Conjunctiva.

Xerosis is usually described as divided into epithelial or primary xerosis, and essential shrinking of the conjunctiva or secondary xerosis. Pathologically the changes in the epithelium may be looked on as identical, except that those in the essential shrinking form are much more marked, and are characterised by the formation of papillæ. Both conditions are due to drying of the epithelium, owing to the deficiency in lachrymal secretion.

In epithelial xerosis the lachrymal secretion is deficient owing to general malnutrition, whilst in the essential shrinking form the deficiency is due to chronic inflammation of the subconjunctival tissue, which contracts around the orifices of the lachrymal ducts, or possibly in some cases to primary degeneration of the gland. As a result of the deficiency of lachrymal secretion the epithelial cells seem unable to form mucin, as in ectropion; this fact, and the changes resulting from it, will be shown in greater detail while describing immediately the two forms of xerosis.

The Primary Form, or Epithelial Xerosis. (*Associated with Night Blindness.*)—Primary or epithelial xerosis associated with night blindness occurs chiefly in children and sailors. The essential point in its production seems to be the want of proper food. It is specially prevalent in Russia

during famines, and is also found in India and other hot climates where evaporation from the conjunctiva would be at its maximum. In these countries it is often associated with marasmus and keratomalacia.

As I have already published the histological changes in six cases elsewhere,[1] I shall only give a brief outline of the histology of the disease.

This disease is characterised by the formation of patches or placques on the ocular conjunctiva. Clinically these placques are situated in the interpalpebral region of the bulbar conjunctiva at either side of the cornea, being more marked and sometimes found only on the temporal side.

The plaques are white in colour, being covered with minute bubbles of Meibomian secretion. That this is the origin of these bubbles is evident from the following facts:—

(1) Their appearance is similar to the beaten-up secretion which occurs at the angles of the lids in chronic conjunctivitis.

(2) If the secretion be wiped away and the lids held apart by a speculum, it does not reform.

(3) In one of my cases which was of long standing the secretion had dried on the surface; there being no bubbles, the fatty secretion could be peeled off and examined.

When this secretion is wiped away it leaves

[1] *Trans. Ophth. Soc.*, 1903.

a dry, slightly wrinkled surface unmoistened with tears, but if thoroughly cleansed by using soap it becomes moist. Smear preparations and cultures from the plaques show the so-called xerosis bacilli together with other organisms (*pneumococcus*, *staphylococcus*, &c.). After fixing the tissue in perchloride of mercury, sections stained by methylene blue, Gram's and Neissler's methods showed xerosis bacilli in the Meibomian secretion adhering in large quantities to the surface of the epithelium; and although a number of the sections made in series were examined, no organism could be found either in or between the epithelial cells, or in the deeper tissue. That the xerosis bacillus is not the cause of the plaques seems evident since:—

(1) It is not found in the tissue of the conjunctiva.

(2) I have examined the Meibomian secretion from twenty cases—ten of normal Meibomian secretion and ten from beaten-up secretion found at the angles of the lids in chronic conjunctivitis. In five of the normal cases I found the bacillus, and also in nine from secretion at the angles of the lids. Deyl isolated the bacilli in fifteen cases of chalazion, and even went so far as to say that this organism was the cause of that disease.

(3) Its behaviour in culture after the initial growth on blood serum is that of a saprophyte.

(4) When inoculated into man or animals it does not reproduce the disease.

From these facts I think that the so-called xerosis bacillus may be looked on as a saprophitic organism occurring in the Meibomian secretion, exactly comparable to the smegma bacillus occurring in the secretion of the glands of the prepuce.

The changes in the epithelium are similar to those brought about by exposure.

The epithelium is thickened, and there is some increase in the subconjunctival tissue beneath. The superficial layers of epithelium show a well-marked layer of keratin on the surface. No fat granules can be demonstrated by staining with sudan III., but there are some granules staining with osmic acid; there is also another set of granules which stain with Gram and Unna's polychrome blue, which are suggestive of the persistence of the prickle cells of the deeper layer in the horny outer layer: some of the nuclei are persistent in this layer.

Beneath this layer of keratin there is a well-marked layer of cells showing granules of kerato-hyalin which stain well both by Ernst's Gram method and by hematoxylin decolourised in permanganate of potash; the former method of these two I found the more reliable. The keratohyalin granules are principally situated in the periphery of the cells, and the protoplasm of the nucleus lies to one side of the nuclear membrane. Beneath

3

this layer of keratohyalin is a well-marked layer of cells showing intercellular bridges, which are best seen in preparations when treated with osmic acid and tannin. Scattered through this layer and the basal layer are nuclei, which hold the stain after prolonged decolourisation and seem to be intensely basic.

Another important point is the complete absence of cells undergoing mucoid change. To show that these formations of keratin, keratohyalin and prickle cells do not occur in normal conjunctiva, I have stained pieces of conjunctiva removed from opposite the palpebral fissures of a child aged 5 and of a man aged 40, and also a pinguecula. In the child aged 5 there was no trace of any of these changes; from the man aged 40 a few scattered cells showed granules of keratohyalin; and in the pinguecula there were a few epithelial cells showing granules of keratohyalin to a greater extent than in the previous cases. There were no prickle cells or keratin formation in any of these.

Keratin when free from fat is itself an hydratible body; that is to say, is capable of being moistened with water or lachrymal fluid, since the lachrymal fluid has a higher surface tension than water. But the least trace of grease in the epithelial cells is sufficient to raise its surface tension and prevent it from becoming moist, while it still allows particles of a higher surface tension than the lachrymal fluid to become adherent to it. A well-

known parallel to this is to take two pieces of steel wire and cleanse them by heating to a red heat, putting one directly into a vessel filled with soda water, but passing the other through the fingers before placing in the soda water; the bubbles of gas adhere to the surface of the wire which has been passed through the fingers, owing to the trace of grease on the wire raising its surface tension and preventing hydration of the surface. In a similar way Meibomian secretion organisms, &c., will become adherent to the keratinised plaques. This Meibomian secretion can therefore be made to disappear either by raising the surface tension of the lachrymal fluid or by lowering the surface tension of the plaques. Mucin is one of the most important factors in bringing about hydration in the normal conjunctiva. Torochlorate of soda derived from bile salts is one of the most powerful agents in reducing surface tension. If two or three drops of a 20 per cent. solution of this substance are instilled into the conjunctival sac in a case of epithelial xerosis, and gentle massage applied, the white patch of Meibomian secretion disappears and the surface becomes covered with lachrymal fluid; this will only take place in mild cases of the disease. In a similar manner if castor oil be instilled, the secretion from the Meibomian glands disappears from the surface of the plaque, but of course this only lasts whilst the oil remains in the conjunctival sac. The surface tension of the lachrymal fluid

estimated by a capillary glass tube which has been thoroughly cleansed by potash and absolute alcohol, is slightly raised in this disease, probably owing to the presence of Meibomian secretion.

I think, therefore, that the essential change in the production of these plaques is the keratinisation of the epithelium, due partly to exposure and partly to deficient lachrymal secretion, occurring in children of delicate health, and that the Meibomian secretion with the bacilli is simply adherent to these plaques owing to the altered surface tension, due to keratinisation of the epithelium and the absence of mucoid change therein.

The Secondary Form of Xerosis, or Essential Shrinking of the Conjunctiva.—It is extremely doubtful if this trouble ever occurs as a primary disease, but is not always secondary to some form of chronic inflammation, which at the time that the disease appears may not be active, as, for instance, in the case of pemphigus when quiescent. (W. Lang, A. Critchett, H. Juler, *Trans. Ophth. Soc.*, 1896.)

Besides pemphigus it follows trachoma, lupus, burns and cicatrices of the conjunctiva; in fact, any disease leading to drying of the conjunctiva, either by direct invasion of the lachrymal gland or by blocking of its ducts from cicatricial contraction.

The change in the epithelium is similar to that previously described in epithelial xerosis, but, in

addition, papillæ of epithelium are formed by the downward growth of the epithelium into the underlying tissue. A case of this kind has been recorded by E. Treacher Collins (*Trans. Ophth. Soc., U.K.*, vol. x., 1890, p. 62), which showed papillæ similar to those formed after the exposure of the epithelium in ectropion.

In a case of lupus associated with essential shrinking I found similar changes in the epithelium.

The condition of the underlying subconjunctival tissue depends on the cause of the disease. In trachoma the trachomatous follicle may be present. In lupus, typical giant-cell systems with epithelioid cells, &c., are found; in pemphigus, fibrous tissue. The plaques seem especially to pick out the more scarred portions of the conjunctiva. In three cases following on trachoma which I have had the opportunity of examining, the changes in the epithelium were exactly similar to those described under epithelial xerosis, with the exception that the basement membrane in one case was extremely thick, the keratinised layer being also very thick. Adherent to the surface was a definite membrane formed of Meibomian secretion and epithelial *débris* (fig. 22). In one case the whole lower palpebral conjunctiva was covered with this membrane, which was very adherent, and when scraped off re-formed in a few days. To this class, I believe, belong some of the so-called membranous conjunctivitis with persistent membranes. (Morton and E. T. Collins, *Trans. Ophth. Soc.*, vol. xiii., 1893).

The Subepithelial Tissue.

Before passing to the description of the changes in the subepithelial tissue, it is necessary to describe in more detail the character of the cells found in the subepithelial layer of the normal conjunctiva.

Description of the Cells forming the Subepithelial Layer. — These consist of three varieties :—

(1) Those of hæmic origin.

(2) Those derived from the connective tissue.

(3) Those of uncertain origin.

Cells of Hæmic Origin.

Polymorphonuclear leucocytes (*neutrophiles*) are found in very small numbers in the subepithelial tissue, but their numbers are enormously increased in any acute inflammatory condition. They exhibit most active movements and are often found making their way between the epithelial cells. It is these cells which are the great phagocytes, and they are often found containing organisms. They are of undoubted hæmic origin, being found in increased numbers in the blood during any active inflammatory process, and are derived from the bone-marrow. When stained by Pappenheim's method the nucleus of the cell stains dark green, whilst the cytoplasm stains either faintly green or not at all. They are practically never found undergoing mitosis in the tissue (pl. i., d).

Spider Cells.—Spider cells are cells of curious

branching shapes which are in reality polynuclear leucocytes fixed in the process of amœboid movement (fig. 34). That this is their origin seems evident because—

(1) They are found principally at the edges of sections where immediate fixation of the tissue would result when placed in the fixing agent.

(2) When examined carefully their elongated nuclei can be made out.

(3) They are found principally in sections of acute inflammatory processes where polynuclear cells are seen (fig. 39).

(4) If the tissue is not fixed rapidly these cells are not seen to nearly the same extent.

(5) They are found especially in the denser tissue, where they cannot assume their rounded shape.

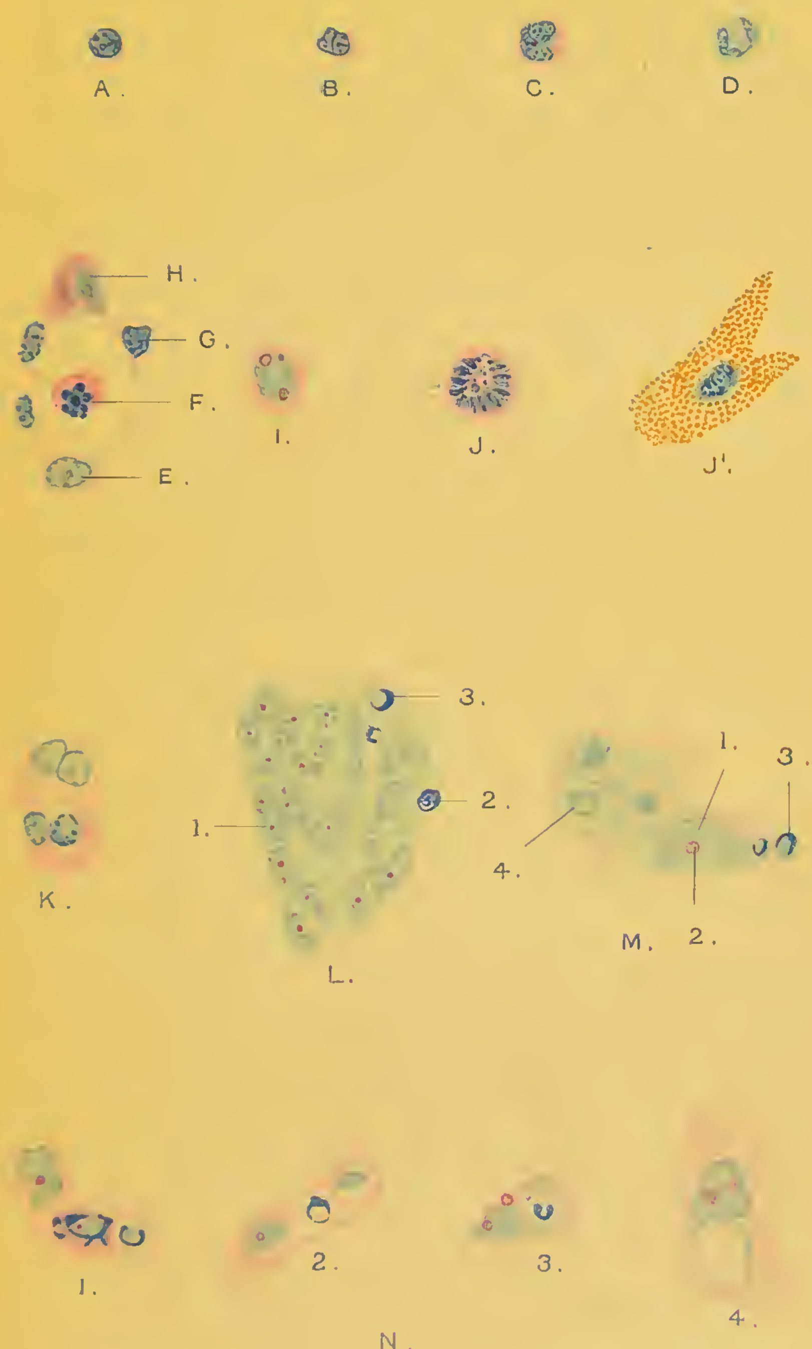
The *polymorphonuclear eosinophile* is not recognisable by Pappenheim's staining, but is easily recognised by staining with logwood and eosin, or one of the eosin-methylene blue compounds. Its cytoplasm contains large granules which are the nodes of the reticulum of the cytoplasm. Like the polymorphonuclear neutrophile, it is of undoubted hæmic origin, being originally derived from the bone-marrow. It is found in scanty numbers in all forms of conjunctival inflammation, but it is found in enormous numbers in pemphigus and spring catarrh.[1] In the latter disease it is of

[1] I have also found them in a case of conjunctival inflammation, probably due to the sting of an insect.

PLATE I.

A, Lymphocyte ; B, transitional ; C, large mononuclear leucocyte ; D, polymorphonuclear neutrophile ; E, F, G, H, showing the origin of the cells from a small vessel within a follicle ; E, endothelial cell which has recently proliferated ; F, plasma cell ; G, ? Lymphocyte, ? endothelial cell ; H, clasmatocyte ; I, clasmatocyte ; J, mitosis in a clasmatocyte, or large plasma cell ; J^1, mast cell ; K, chorioplaque (giant cell, plasma cell type) ; L, giant cell, endothelial type—(1) nucleus-like endothelial cell, (2) inclusion (nucleus of lymphocyte), (3) coccoid body of Leber (disintegrating cell inclusion) ; M, large phagocytic endothelial cell—(1) nucleus, (2) nucleolus, (3) Leber's coccoid body, (4) disintegrating lymphocyte ; N, showing the various stages of digestion of a plasma cell by an endothelial phagocytic cell (1) an inclusion of a plasma cell, (2) plasma cell breaking up, (3) coccoid body formed of nucleus, (4) vacuolisation. (Pappenheim's stain.)

PLATE 1.



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great diagnostic value when associated with the clinical condition (fig. 42).

Basophile mast cells are found but rarely in normal conjunctivæ. They are large cells and have probably very amœboid movements. Their cytoplasm consists of large coarse granules which stain best with Unna's polychrome blue (bright red) or with Pappenheim's stain (orange). The nucleus is granular and stains blue. These cells are found in large numbers in the fibrous tissue after chronic inflammation and in phlyctenulæ in their healing stage and seem to be identical with those found in the blood (pl. i., fig. 5).

Connective Tissue Cells.

Connective tissue cells in the conjunctiva are of two types: those of the (*a*) *deeper layer*, which are elongated and of a wavy outline and arranged parallel to the surface. With Pappenheim's method the nucleus stains blue, with the nucleolus staining bright red. The cytoplasmic tails also stain pale red. In this layer of the normal conjunctiva there are, comparatively speaking, no other cells but these, except perhaps an occasional plasma cell or leucocyte (fig. 24, c).

(*b*) In the *superficial layer* the cells become of a much larger type and stain more darkly. Their shape is oval and the protoplasm better marked. The nucleus and protoplasm stain blue, with a

bright red nucleolus. They have often no tails or only very small ones.

The endothelial and perithelial cells of the blood-vessels are flattened in the capillaries of the superficial layers of connective tissue in the normal conjunctiva. They stain dark green, like some of the connective tissue cells, with a red nucleolus. Directly any proliferation takes place they become larger and more rounded in shape, either bulging into the lumen of the blood-vessel or protruding externally. Their cytoplasm takes up the pyronine of the Pappenheim stain much more readily (pl. i., fig. H E). They migrate into the surrounding tissue, undergoing mitosis, and when in that stage are indistinguishable from the plasma cell, from which, I believe, this cell is derived (pl. i., fig. I). Against this it must be remembered, as has been pointed out by Whitfield, that there is no distinctive stain for plasma cells, and that any young cell takes on a basic staining reaction, and that therefore the recognition of a plasma cell also depends on the characteristic appearance of its nucleus, which is destroyed by the mitosis taking place. But this point, I think, shows the possibility of the formation of a plasma cell from the endothelium or perithelium of vessels. These round, darkly staining migrating endothelial cells seem to be identical with the cells called clasmatocytes by Ranvier and Marchand, which name I therefore shall adopt in speaking of them.

The endothelial cells are also strongly phagocytic and there are often cell inclusions (pl. i., fig. M N).

Cells of Doubtful Origin.

Lymphocytes are divided into large and small, the large cell being the smaller cell in a more highly developed state. Their nucleus stains dark blue with Pappenheim, whilst the cytoplasm stains pale red. They are formed in the follicles of the lymphatic glands, probably from their endothelial lining, and from thence are carried in small numbers into the blood stream ; but, unlike the polynuclear leucocytes, they are not increased in the blood in inflammatory conditions (absence of chemiotaxis), although enormous numbers are found at the site of inflammation, so that they must be produced locally by rapid division of the few cells brought by the blood stream, as is held by some observers, or else from the endothelium of the part, which, I think, is more probable.

The relation of the large mononuclear leucocyte to the lymphocyte is at present doubtful ; but since they are found together wherever they occur and the staining reaction of their cytoplasm is the same, although the nucleus is of a slightly different shape, I think that they probably belong to the same generic type. The large mononuclear leucocyte is very difficult to recognise in tissue, it being confused on the one hand with the clasmatocyte, and on the other with the large lymphocyte. Even

in smear preparations of the fluid taken from serous cavities it is often difficult to distinguish between the wandering endothelial cells and the mononuclear leucocyte, although this difficulty is not admitted by some of the authorities. It is therefore obvious that its recognition in the tissue is so much the more difficult. It is admitted by all pathologists that the lymphocytes and the large mononuclear cells are intimately related to the plasma cell, and are always found together, although either may be in excess (pl. i., figs. A B C).

Plasma Cells.—Of all cells found in the body perhaps none has given rise to so much discussion with regard to its origin as the plasma cell. Unna, who brought this cell into so much prominence, holds that it is derived from the connective tissue. Other observers say that it is derived directly or indirectly from the lymphocytes.

Although the plasma cell has perhaps been given undue prominence, it is without doubt one of the most important cells in conjunctival inflammation. It is found normally in small numbers in the conjunctiva beneath the epithelium, and its numbers are greatly increased in all inflammatory affections, especially in those of the more chronic type, such as trachoma.

Its situation when present in large numbers is chiefly around the vessels, and hence its position in the superficial layers of the subepithelial tissue. It seems to be slightly amœboid, but not nearly to the same extent as the polynuclear leucocytes.

When stained by Pappenheim's method the cytoplasm stains a uniform dark red without granules, whilst the nucleus stains dark blue and is very granular, containing a nucleolus, which stains red. There are always to be found cells which pass in staining reaction into the lymphocytes on the one hand, to which they are very closely allied, and into the endothelial or perithelial cells on the other (pl. i., fig. F).

In addition to the above cells, which are found in normal conjunctivæ, there are two types of cells which are formed only in inflammatory conditions.

Epithelioid Cells. — These cells are found in trachoma, tubercle, leprosy, syphilis, &c., and are arranged round the foci of the disease. Outside them there is always a layer of mononuclear leucocytes, from which they are most probably derived by the action of the toxins on the mononuclear leucocytes. In structure they are intermediate between the wandering endothelial cells (clasmatocytes), and the large lymphocytes.

Giant Cells.—Giant cells in the conjunctiva are of two types :—

(1) *The chorioplaques*, which are derived from the plasma cells, most probably by incomplete division of the cytoplasm. These cells are found in all inflammatory conditions of the conjunctiva (pl. i., fig. K).

(2) *Giant cells proper.*—The giant cells proper are always more or less rounded in the conjunctiva,

owing to the laxity of the tissue, and are derived from the endothelial cells by division of the nuclei, with imperfect division of the cytoplasm. These cells are probably due to the action of the toxins producing cell monstrosities. They occur frequently in all chronic inflammatory conditions of the conjunctiva, around foreign bodies, &c., the conjunctiva having a great proclivity to form this cell. Like the endothelial cells they are also phagocytic (pl. i., fig. L).

These two types of giant cells stand in the same relation to one another as the plasma cells and the endothelial cells, from which they are respectively derived, do to each other.

LECTURE II.

Traumatic Conjunctivitis, with Special Reference to the Changes in the Cellular Elements as the Result of Wounds.

Wounds of the Conjunctiva.

Wounds of the conjunctiva occur as the result both of injury and of operation. Since the introduction of conjunctival flap operations for cataract and glaucoma, a knowledge of the process of healing is of greater importance, as after the flap is made the wound in the globe is shut off by it from direct communication with the conjunctival sac. Wounds in the conjunctiva are made also for the purpose of tenotomy, advancements, &c.

Further, the conjunctiva of the bulb being largely free from cellular elements, it offers one of the most favourable situations for the study of the early changes of traumatic inflammation, more especially as regards the formation, destination, &c., of the plasma cells, since these latter are of such frequent occurrence in all inflammatory conditions of the conjunctiva.

In the course of some other work the following experimental wounds were made on rabbits. At definite periods these wounds were carefully removed, fixed in alcohol, embedded in paraffin, cut transversely to the wound in serial section, and stained with logwood and dilute eosin, and by Pappenheim's stain; the logwood and eosin showing the character of the cells with regard to their nuclei and the acid granules of their cytoplasm, whilst the pyronine and methyl green of the Pappenheim stain showed the plasma cells and the various types of connective tissue cells, bacteria, &c.

A preparation of rabbit's blood was made by fixing drops of blood in alcohol, embedding in paraffin and staining by Pappenheim's method—adopting, in fact, the same process as that by which the sections of tissue were prepared.

Experiment No. 1.—A piece of normal conjunctiva removed from the ocular portion of the membrane above the cornea.

The normal conjunctiva of a rabbit is covered externally by *epithelium* some three or four cells in thickness. The deeper cells are of somewhat oval shape, arranged with their long axis parallel to the surface. Above these are a number of cells of irregularly rounded outline. On the surface the cells become somewhat flattened. Numbers of these cells undergo mucoid change, which somewhat distorts the cells lying in contact with them. Every here and there between the

cells, especially in the deeper layers, are found leucocyctes, which are principally of the polynuclear type, a few being lymphocytes.

On the surface and between the superficial cells are found a number of bacteria, both cocci and bacilli, a description of which has been given by Randolph (*Johns Hopkins University Medical Journal*, 1903).

THE SUBEPITHELIAL TISSUE.

Superficial Layer.—Directly beneath the epithelium the connective tissue is loose in structure and contains numerous blood-vessels, lymphatics and nerves. Its cells are more rounded than those of the deeper layer, having an oval nucleus with one or two nucleoli. When stained by Pappenheim's method the nucleus stains pale blue and the nucleoli are red. Scattered principally around the vessels are a few plasma cells, their cytoplasm staining bright crimson, without granules, the nucleus being dark blue and showing coarse granules, the nucleolus staining red. Some of these cells show mitotic division. There are also a few lymphocytes, both small and large, and some polynuclear leucocytes. Various cells, intermediate in their staining reaction between the plasma cells and the endothelium of the blood-vessels on the one hand, and between the plasma cells and the

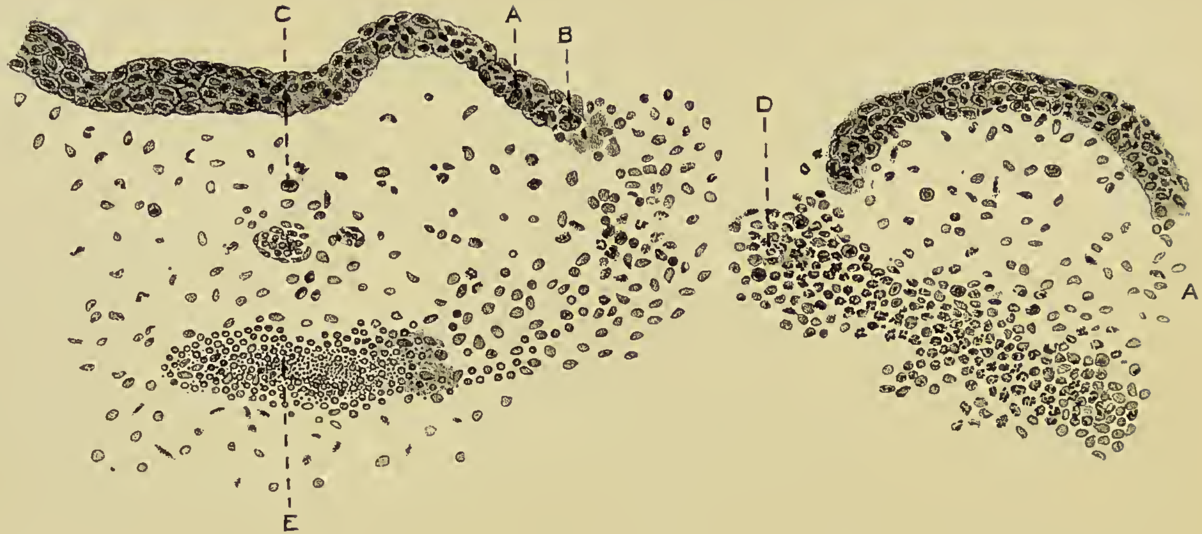

FIG. 23.—Wound of the conjunctiva after six hours. A, Corneal side of the wound; A-, epithelium infiltrated with polynuclear leucocytes; B, epithelial cells which are undergoing necrosis from the injury; C, plasma cells; D, polynuclear leucocytosis; E, blood containing dirt and organisms. *Note* that there is practically no increase in the plasma cells. $\frac{1}{12}$ obj. No. 2 eyepiece.

large lymphocytes on the other hand, are to be found.

Deep Layer.—Beneath the superficial layer is one of denser connective tissue, the cells of which are of a very elongated spindle shape. There are practically no leucocytes or plasma cells in this layer. Beneath it, again, are a few unstriped muscle fibres, which lie directly over the episcleral tissue.

Experiment No. 2.—A horizontal wound 1 cm. long was made in the bulbar conjunctiva above the cornea, about 3 mm. from the corneo-scleral junction.

This wound was examined after six hours had elapsed. The edges had retracted about 2 mm. There was a slight hæmorrhage into the upper lip of the wound at the time of the operation. The wound had shown no tendency to adhere to the underlying sclera (fig. 23).

Microscopical Examination.—The *epithelium* near the margins was curled down over the edge of the wound and was infiltrated by leucocytes. A few of the epithelial cells at the edge had become separated, probably at the time of the injury, and had swollen up, their nuclei being indistinct and not taking the stain well; they were evidently necrosing. Otherwise there was no evidence of proliferation of the epithelium.

Subconjunctival Tissue.—The vessels showed no marked signs of dilatation. In the region of

the wound a quantity of lymph had been thrown out, which was packed with leucocytes, almost entirely of the polynuclear variety. Both in this and in the surrounding tissue there was a slight increase in the number of plasma cells ; none of the connective tissue cells had shown any signs of change. The changes above described were more marked on the corneal than on the conjunctival side of the wound. The extravasated blood contained a number of particles of dirt and bacteria, these latter being principally cocci, with a few scattered bacilli. The bacteria and particles of dirt were limited to the extravasated blood, none being found in the surrounding tissue.

Experiment No. 3.—A horizontal wound 1 cm. long made in the ocular conjunctiva 4 mm. from the corneo-scleral margin above, and examined after twenty-four hours' duration. The wound had not retracted to the same extent as in the last case (fig. 24).

Microscopical Examination.—The *epithelium* had commenced to grow down over the edges of the wound. The newly-formed epithelium was thinner than the old epithelium beyond the wound, the junction between the two being fairly well defined. Along the new epithelium there were in places irregular thickenings, which dipped down into the adjacent subconjunctival tissue in papilla - like processes.

At the spreading margin of the epithelium the

FIG. 24.—Wound of the conjunctiva, twenty-four hours. A, Epithelium ; B, superficial layer of connective tissue (*note* the swelling) ; C, deep layer of connective tissue ; blood-vessels ; E, cut ends of the deep layer of connective tissue ; F, proliferating connective tissue cells, principally from the underlying episcleral tissue ; G, mononuclear leucocytes and plasma cells around the dilated vessels ; H, polynuclear exudation adherent to the wound ; I, vessel of new formation with proliferating endothelium ; J, an enormous exudation of plasma cells and mononuclear leucocytes around a portion of Krause's gland, which has come into the base of the wound. It was impossible to draw this in proportion to the rest of the drawing, owing to the number of cells.

cells were often only a single layer in thickness. Occasionally the spreading margin terminated in a clump of epithelial cells, giving rise to the papilla-like processes before described. This thickening always takes place when there is an obstruction to the spread of the cells along the surface of the wound, such as would be caused by a mass of lymph, the epithelial cells trying to make their way either above or below the obstruction, which, becoming organised, gives rise to the papilla-like processes described.

The *subconjunctival tissue* shows marked changes. The vessels in the neighbourhood of the wound are dilated to an enormous extent, and the endothelium is proliferating. The connective tissue spaces are widely separated by lymphocytes and œdema. This swelling takes place almost entirely in the superficial part of the conjunctiva, the comparatively non-vascular layer of connective tissue showing little change. There is also a great increase in the plasma cells, which lie principally around the blood-vessels of the superficial layer, there being practically none in the connective tissue of the deeper layers. The leucocytes, which are present in large numbers in the edges of the wound, are almost entirely of the mononuclear variety.

It will be noted, therefore, that the exudation has changed from that containing cells which in the wound just described, of six hours' duration, were principally polynuclear leucocytes, to that

consisting almost entirely of mononuclear forms; and that, coinciding with the change, there is a large increase in the plasma cells, which are found in the lymphocytic exudation. In the fibrin between the lips of the wound can still be seen the polynuclear leucocytes of the original exudation. The cells of the divided edges of the connective

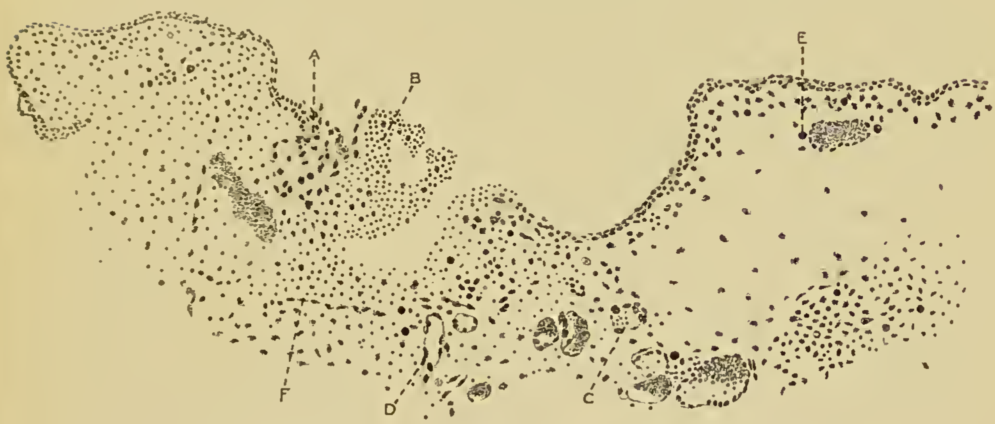

FIG. 25.—Wound of the conjunctiva, forty-eight hours. A, Epithelium which is proliferating at its spreading margin, and has become heaped up in consequence of obstruction to its spread by the mass of exudation in the wound B; C, vessel showing diapedesis; D, vessel of new formation showing proliferating endothelium; E, plasma cells.

tissue in the deeper part of the wound have become more spherical in shape and are proliferating; although proliferating, there are practically no plasma cells in the neighbourhood of this tissue.

In some of the sections a portion of Krause's gland has become incorporated in the base of the wound, and around it there is considerable

exudation of mononuclear leucocytes and plasma cells. The vessels on the corneal side of the wound contain a greater number of leucocytes and plasma cells in proportion to their size than those on the side away from the cornea.

Experiment No. 4.—A horizontal wound rather less than 1 cm. long was made 3 mm. from the corneo-scleral junction, above the cornea. The wound was examined after forty-eight hours interval (fig. 25).

The *epithelium*, like that in Experiment No. 3, is gradually spreading across the wound, and is to some extent obstructed by the adherent fibrin, so that the growing ends consist of irregular masses of epithelial cells, which subsequently form peninsula-like processes, as will be seen later. These young cells take up the Pappenheim stain readily. The adherent fibrin in the wound contains leucocytes, some of which are degenerating

The Subconjunctival Tissue.—The vessels, although still somewhat dilated, are reduced in size. The endothelium is proliferating, and there are a quantity of newly formed vessels in the wound, many of which show beautiful examples of diapedesis. The lymphocytes have mostly disappeared from the base of the wound. The true plasma cells have also practically gone, except a few in the region of the vessels and lymphocytic exudation, although several of these cells can still be seen which have undergone degenerative changes.

The base of the wound is filled with young connective tissue cells, derived from that overlying the sclera and from the cut edges of the connective tissue. In it are a quantity of the newly formed vessels already described, so that if there is a wound into the globe it will now be shut off

FIG. 26.—Wound of the conjunctiva 120 hours. A, Epithelium dipping down, in papilla-like process, into the subepithelial tissue: B, masses of epithelial cells in the underlying tissue, due to the bulbous end of the papilla-like process. When followed through series of sections they are, however, usually found connected with the surface epithelium; C, mononuclear exudation with plasma cells; D, dilated vessel.

externally by the attachment of the conjunctival flap to the underlying episcleral tissue, even before the wound has entirely healed; this sealing off of the wound takes place in the rabbit in forty-eight hours.

Experiment No. 5.—A horizontal wound 1 cm. long was made in the ocular conjunctiva 3 mm. from the cornea-scleral junction, above the cornea. The wound was examined one hundred and twenty hours after being made (fig. 26).

Microscopical Examination.—The *epithelium* has completely covered the wound and the surface is thrown into folds, which are no doubt due to the contraction of the newly formed fibrous tissue. By far the greater part of the epithelium of the wound has united with that of the opposite side. In one portion of the wound the epithelium of one side has dipped down, and the epithelium of the other side growing across has failed to meet it, with the result that there has been proliferation of the dipping-down epithelium, forming numerous peninsula-like processes in the subconjunctival tissue. The subconjunctival tissue just around this growing-down process is "rarified," and more or less free from cellular elements.

The *subconjunctival tissue* is largely free from mononuclear cells except in the base of the wound, where there are several large collections of these cells, and there are often similar collections beneath the epithelium. In these situations there are still some plasma cells, but elsewhere they have disappeared, with the exception of a few undergoing degenerative changes ; plasma cells are still to be found within the vessels. The newly-formed connective tissue cells become gradually more spindle-

celled in shape and begin to resemble the connective tissue cells in the normal conjunctiva; they are, however, still increased in number, more closely packed together, and at the same time undergoing proliferation. There are still a number of newly-formed vessels to be seen at the site of the wound. In the deeper parts of the wound are to be found a number of giant cells of the chorioplaque type, which seem to be derived from the plasma cells, their nuclei and staining reaction being of much the same character.

Experiment No. 6.—The wound produced by the removal of the piece of conjunctiva in Experiment No. 1, which has healed after one hundred and seventy hours, was then examined.

The *epithelium* had completely regenerated on the surface, and like the old conjunctival epithelium was beginning to show signs of mucoid change.

The *subconjunctival tissue* contained a few lymphocytes in excess of the normal number. The plasma cells were not more numerous than those found in the normal conjunctiva. The connective tissue cells were still somewhat increased in size, but were rapidly approaching the appearance of those in the normal conjunctiva. There were a few giant cells, with nuclei identical with those of the endothelial cells, from which they are derived.

The blood-vessels were somewhat dilated, and there were still a few patches of lymphocytic exudation, which were probably attempts at folli-

cular formation. Otherwise the whole appearance of the wound resembled very closely that of the normal conjunctiva.

Conclusions Derived from the Study of the Above Sections.

(*a*) *Regeneration of the Epithelium.*—As the result of the contraction of the underlying elastic tissue the edges of the epithelium are turned downwards. As the result of the injury a few of the epithelial cells at the edges of the wound are killed, swell up, degenerate, and are probably either absorbed by the leucocytes or cast off in the discharge.

The infiltration of the epithelium with leucocytes and plasma gives increased nutrition to the cells and therefore promotes their rapid division and spread, and further, by the phagocytic power of the leucocytes the destruction of organisms lying between the cells is carried on—a most important point, because although the conjunctiva always contains organisms, it is very rarely that a wound of it becomes septic.

Proliferation of the epithelium does not seem definitely to commence at the margin of the wound for at least twenty-four hours, nor could I find any evidence of it elsewhere beyond. The spreading margin is generally one cell deep, thickening taking

place rapidly, as the growth of epithelium progresses across the wound. Should the growing epithelium meet obstacles, such as an exudation of lymph, in its endeavour thus to cover the surface, it becomes thickened, producing the peninsula-like processes which eventually dip down into the adjacent sub-conjunctival tissue and which are often only attached to the surface epithelium by a thin band. It is conceivable that if this band of epithelium subsequently atrophies, from pressure of the contracting fibrous tissue, it may leave a collection of epithelial cells in the deeper tissue which might become the seat of an implantation dermoid or even undergo malignant change. If the epithelium does not meet on the two sides the healing of the wound may be greatly delayed. The epithelium covers small incised wounds of the conjunctiva in one hundred and twenty hours.

(*b*) *Changes in the Subconjunctival Tissue.*—When the ocular conjunctiva is divided it retracts, owing to the elastic tissue in its substance. The underlying episcleral connective tissue coming into the base of the wound, the conjunctiva becomes firmly adherent to it in forty-eight hours, so that, arguing from analogy, it may be concluded that after a flap operation for cataract the wound is usually shut off from the conjunctival sac in that time.

Usually some hæmorrhage occurs in which organisms seem to have the power to live, but

any which gain entrance to the subepithelial tissue, except those in the blood clot, are taken up by the polynuclear leucocytes, unless the wound becomes septic. A practical point, therefore, is to remove from wounds of the conjunctiva as much blood clot as possible.

The leucocytes exuded during the first twenty-four hours are chiefly of the polynuclear type, and these cells possess a highly phagocytic power. After the first twenty-four hours, provided the wound be comparatively aseptic, the exudation consists practically of mononuclear cells only.

Coinciding with this appearance of the lymphocytic exudation in the wound there is a large increase of plasma cells. These latter cells and the lymphocytes appear around both the large and small vessels on *both* sides of the wound, which at this time have actively proliferating endothelium, and on the side away from the cornea are dilated to their fullest extent; they are also seen around the endothelium and perithelium of the gland tissue which has become incorporated in the base of the wound. The connective tissue cells at the deeper part of the margins of the wound show signs of proliferation. But although there is proliferation of these cells there are no plasma cells or mononuclear leucocytes in their neighbourhood.

In the wound of forty-eight hours' duration the plasma cells have decreased in number and are

mostly undergoing degenerative changes; whereas, on the other hand, the connective tissue cells are showing the greatest signs of proliferation, without forming true plasma cells such as are found in the exudation of lymphocytes, although a few scattered plasma cells can be found in the neighbourhood of the new vessels.

In the wound of one hundred and twenty hours' duration there are practically no well-formed plasma cells, except in situations where there is an exudation of lymphocytes.

From all these observations, therefore, it appears to me that the origin of the true plasma cell is probably not the connective tissue cell, but with the lymphocyte, directly or indirectly, in the process of formation from the endothelium or perithelium.

To recapitulate:—

(1) The plasma cells make their appearance at the time when lymphocytes appear in the wound, and it is then that they are found in the greatest numbers; the connective tissue cells in the deeper parts of the wound, although commencing to show changes, have practically no plasma cells around them, which seems to me strongly against their origin from the fixed connective tissue cells, but where the perithelium covering the gland tissue comes into the base of the wound it is packed around with plasma cells and mononuclear leucocytes.

(2) They are arranged principally around the blood-vessels on both sides of the wound, that is to say, around those containing blood and those containing practically no blood, and are also found within them. Many of the vessels around which the plasma cells and mononuclear leucocytes are found have such thick walls that it is impossible to suppose that they have come through their walls.

(3) They begin to disappear in forty-eight hours, when the lymphocytes decrease, and persist in any number only at the actual site of exudation of lymphocytes.

(4) When the connective tissue cells show the greatest activity the plasma cells have to a large extent disappeared, and the majority of those which remain show signs of degeneration.

These facts being taken in conjunction with the fact that all stages of the development of plasma cells are to be observed from the endothelium, and also that, as will be shown, in the lymphatic glands, in which the mononuclear cells are produced, there are found plasma cells, I think the evidence is strongly in favour of the origin of the plasma cell being with the mononuclear leucocyte from a common source, most probably the endothelium or perithelium.

Against the view of the origin of the plasma cell being the endothelium, I have examined sections from the pleura of a rabbit injected forty-eight hours previously with paraffin. The section showed

much proliferation of the endothelial cells on the surface, but there were no definite plasma cells lying between them. Directly beneath there were considerable numbers of plasma cells. J. Briscoe,[1] in examining the fluid from the peritoneal cavity of rabbits at various periods after the injection of normal saline solution, was unable to find any plasma cells. Further, in examining some fifteen cases of eyes enucleated for various acute inflammatory troubles, I have never been able to find any plasma cells free in the anterior chamber, but in one case of chronic iridocyclitis there were numerous plasma cells present in the deposit on Bowman's membrane. This seems to point to the fact that it requires a special type of inflammation, usually of the chronic variety, for the production of plasma cells in serous cavities.

Chorioplaques.—This form of giant cell appears in the peripheral parts of the wound in about one hundred and twenty hours. It is rounded in shape, no doubt owing to the laxity of the connective tissue, and is derived from the plasma cell, its staining reaction and nuclear figure being similar. It appears as the plasma cells begin to disappear from the wound.

Giant cells proper, which have nuclei similar to the endothelial cells, are also seen in the wound of one hundred and seventy hours' duration.

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[1] J. Orth, *Feschrift.*

They are evidently derived from the proliferating endothelium by the division of their nuclei without division of their cytoplasm. Thus in these two cells we have further evidence of the possible relation of the plasma cell to the endothelial cell.

The Blood-vessels. — The blood-vessels show signs of commencing dilatation in six hours, and at the end of twenty-four hours they seem to reach the maximum. The leucocytes are found principally around their walls, that is to say, in the periphery of the blood stream, and the mononuclear varieties are more numerous within the vessels on the corneal side of the wound than in those on the other side. Cells identical in structure with lymphocytes and plasma cells can be seen budding off from their walls at the end of twelve hours; at the same time the endothelium shows signs of proliferation, and at the end of forty-eight hours, a quantity of newly-formed vessels appear in the base of the wound.

Implantation Cysts or Dermoids of the Conjunctiva.

Implantation dermoids of the conjunctiva arise by two distinct methods:—

(*a*) By the downgrowth of the surface epithelium of the conjunctiva, following a wound of that membrane, the connection with the surface epithelium being cut off by atrophy, due to

pressure of the newly-formed fibrous tissue. That this method of formation no doubt not infrequently occurs I have shown already when speaking of wounds of the conjunctiva.

(*b*) Direct carrying in of the conjunctival epithelium by a foreign body. That this method of formation does occur has not been previously proved beyond doubt, as in the two cases which have been investigated by Collins[1] and Lange[2] the cysts were not cut in serial section, so that positive evidence that there was no connection with the surface epithelium was wanting, and the length of time existing between the injury and the examination of the specimens may have caused its disappearance if present.

I had the opportunity of examining a case one week after the bulbar conjunctiva was injured by a chip of wood striking it. The following are the notes of the case :—

F. M., male, aged 11. On November 2, 1902, five days before being seen, the patient was breaking a piece of wood and a piece flew up and struck him in the right eye. It pained him at the time, but he did not take much notice of it till two days later. A "blister," as his mother described it, appeared on the outer side of the right eye. On examination, on the outer part of the bulbar conjunctiva, about 6 mm. from the limbus in the palpebral aperture, there was

[1] Collins, E. T., "*Researches Ant. and Phys. of the Eye*," 1896.
[2] Lange, "*Zehender's Klin. Mon. für Aug.*," xli., 1903.

a red swelling having the appearance of a large phlyctenule. There was no photophobia, and the conjunctival injection was more or less limited to the area surrounding the swelling. No foreign body could be seen. As its nature was doubtful it was excised. It was not adherent to the underlying sclera. A stitch was put in and the wound healed by first intention.

FIG. 27.—Implantation dermoid. A, Epithelium ; B, entrance wound ; C, epithelium lining the cyst ; D, piece of wood within the cyst ; E, blood-vessel of new formation (see plate v.) ; F, blood-vessels surrounded by plasma cells and lymphocytes. (For detail changes, see plate v.).

The specimen was hardened in alcohol and serial sections made, staining with logwood and eosin, and by Pappenheim's method (fig. 27). The wound on the surface had not become completely covered with epithelium, but beneath the gap in the epithelium there was newly formed fibrous tissue.

The position of the cyst with regard to the entrance wound was somewhat oblique, the piece of wood having evidently passed obliquely beneath the surface epithelium. Inside, the cyst contained the splinter of wood causing the injury, as well as many mononuclear and polynuclear cells of all types, a few degenerated plasma cells, and one or two giant cells (pl. v,). The epithelium lining the cyst was for the most part three or four cells in thickness, of the type found on the surface of the bulbar conjunctiva. It surrounded the wood with the exception of a small area opposite the entrance wound, the epithelium evidently having been carried in front of the splinter and then grown round it, as there was evidence of recent mitosis having occurred in the cells at the ununited ends. No process of epithelium could be found connecting the surface epithelium with that of the cyst in any of the sections. Around the cyst there were numerous new and dilated vessels which showed enormous proliferation of their endothelium, and very active diapedesis taking place. The tissue also around the cyst contained numerous leucocytes, plasma cells, and giant cells. The exudation was situated around the vessels, many of these vessels having both endothelial and perithelial coats and some intermediate tissue; in fact, their walls were of such thickness that it is impossible to believe that cells having so little amœboid movement as lymphocytes and plasma cells can have made their way through their walls.

PLATE V.

Implantation Dermoid of the Conjunctiva (see Fig. 27).

Fig. 1.—The epithelium of the cyst wall at the point marked C (fig. 27). F, Giant cell ; G, epithelium on the inner side of the cyst wall. Many of the cells show signs of recent division, and in some instances have two nuclei.

Fig. 2.—H, Portion of the wood within the cyst ; I, endothelial cells and giant cells ; I′, polymorphonuclear leucocyte ; I″, polymorphonuclear leucocyte, staining brown, due to the absorption of material from the wood ; J, mononuclear leucocytes, some of which also stain brown like the polymorphonuclear leucocytes.

Fig. 3.—Portion of a vessel and its contents at the position marked E (fig. 27). K, Endothelium of the vessel wall ; L, leucocytes, many of which are stained brown like those found around the wood (L′) ; M, mitosis in a perithelial cell. This cell is practically indistinguishable from a plasma cell in the specimen.

Fig. 4.—Portion of the wall of an implantation cyst of some standing. A, Surface epithelium of the conjunctiva ; B, subepithelial tissue ; C, tuft-like process of epithelium lining the cyst wall ; D, cells undergoing mucoid change, supplying the interior of the cyst with fluid.

PLATE 5.

Fig. 1.

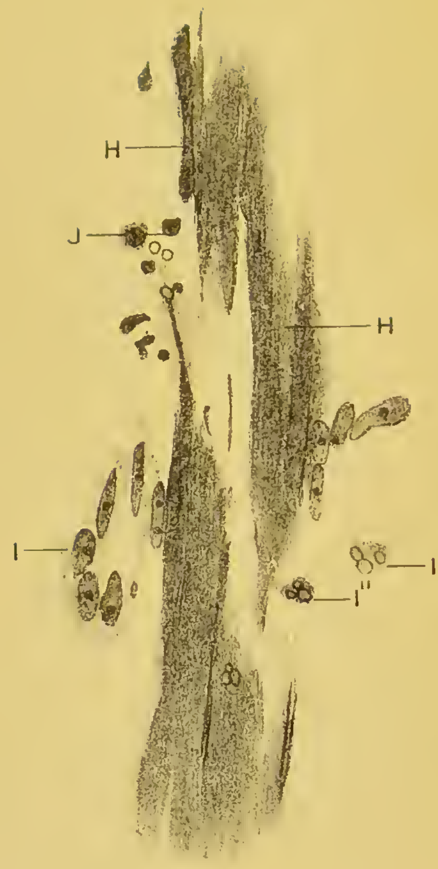

Fig. 2.

Fig. 3.

Fig. 4.

Bale & Danielsson L.td lith.

Another curious point was that some polymorphonuclear, and even some of the mononuclear cells were stained a brown colour. These cells were lying side by side with normally staining cells. They were found in greatest numbers near the chip of wood, to which their brown colour was evidently due, but they were also found in the vessels in the neighbourhood of the wound. If this was due to the ingestion of some material (tannin?) from the wood *ante mortem*, some of the polynuclear cells must have made their way back into the vessels, which is against the generally accepted view. But much stress cannot be put on this, as it is possible that it may have been produced *post mortem*, although the general appearance did not suggest it, since the brown cells lay side by side with normal staining cells.

The fact that there was no process of epithelium connecting the surface epithelium with the epithelial cyst wall, and that the cyst wall was even deficient towards the surface wound in an implantation cyst of such an early date as this, is proof against the theory that all these implantation dermoids are due to downgrowth of epithelium from the surface; and although the other form of implantation dermoid does undoubtedly occur, carrying in of the epithelium also takes place.

Lymphoid Tissue of the Conjunctiva.

At birth, as has been seen, there is no lymphoid tissue in the conjunctiva. That is to say, the cellular elements are absent, although the connective tissue in the fornices is very loose in structure. I have examined a number of con-

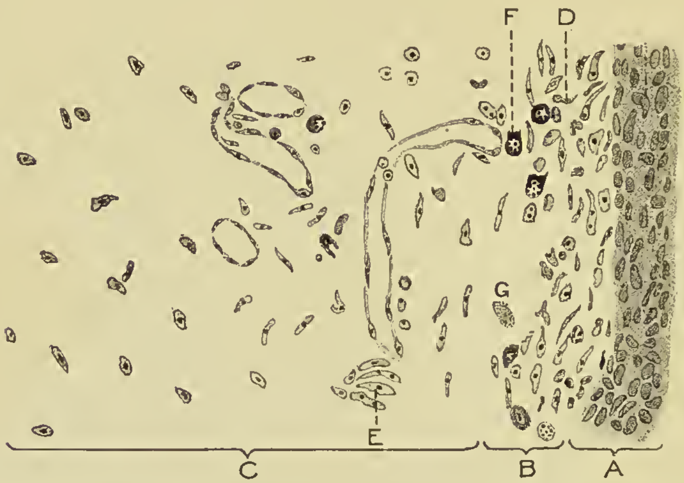

FIG. 28.—Portion of the superior fornix from a child, aged 2 weeks. A, Epithelium; B, layer of mononuclear cells (lymphoid tissue); C, deep connective tissue layer; D, a few polynuclear leucocytes; E, endothelial cells; F, plasma cells; G, mast cell. *Note*, mononuclear leucocytes and plasma cells appear in the neighbourhood of the vessels, beneath the epithelium.

junctivæ removed after death from children of various ages, from birth up to the fourth week, in which, so far as could be ascertained, there had been no previous inflammation, nor any silver nitrate or other irritant applied at the time of birth.

At birth the tissue is entirely free from lymphocytes and plasma cells. There is no evidence of the so-called germ areas of Ribbert, and hence I think it is possible to exclude this theory in dealing with the conjunctiva. After the first few days these cells begin to appear, chiefly around the vessels of the superficial layer in the superior fornix,

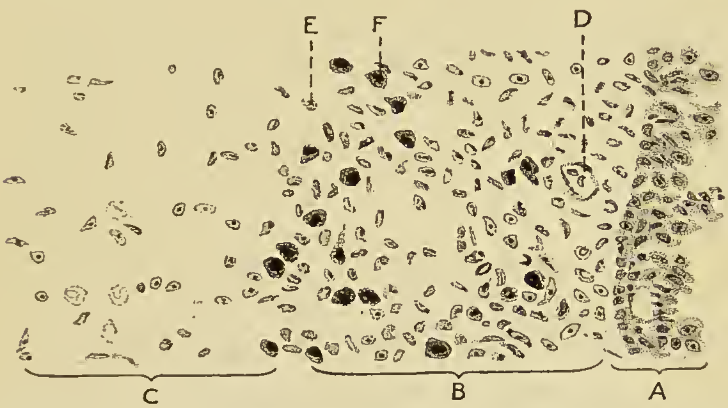

FIG. 29.—Portion o the superior fornix from a child, aged 4 weeks. A, Epithelium; B, layer of lymphoid tissue; C, deep layer of connective tissue; D, small vessel; E, lymphocytes; F, plasma cells. There was no history of discharge in either of these children, the patients being in-patients of the hospital before death. No silver nitrate was applied at the time of birth.

but also, to a less extent, around the deep vessels; these cells gradually increase up to the fourth week, when the lymphoid layer seems to be fully developed (figs. 28, 29).

The fact that these cells appear first in the fornix is probably due to the extreme richness of its tissue in endothelium and perithelium as compared with the palpebral and bulbar conjunctivæ; the rapidity

with which they form depends on the amount of irritation the conjunctiva receives, for if silver nitrate be applied at birth the lymphoid cells appear in forty-eight hours and all the endothelium of the vessels is found proliferating (fig. 30).

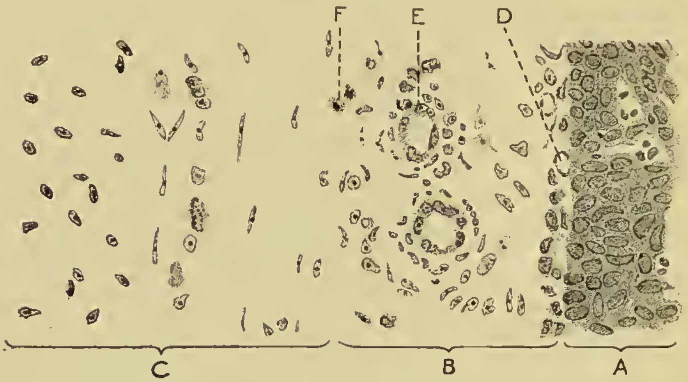

FIG. 30.—Portion of the superior fornix from a child one day old who had a 2 per cent. solution of nitrate of silver applied at the time of birth, showing the exudation caused thereby. A, Epithelium containing polymorphonuclear leucocytes and showing extensive degenerative (mucoid) changes; B, lymphoid layer; C, deep connective tissue layer; D, small vessels beneath the epithelium, many of which are newly formed, with proliferating endothelium giving rise to mononuclear eucocytes and plasma cells; E, large vessels with mononuclear eucocytes around; F, mast cell. $\frac{1}{12}$ obj. No. 4 eyepiece.

If we look at lymphoid tissue elsewhere at birth, such as in the tonsil or the lymphatic glands, we find it full of mononuclear leucocytes and plasma cells. The cells are present for some weeks before birth and are evidently produced in these structures, probably from their endothelial lining.

Going further afield, we find that any connective tissue which is chronically inflamed becomes filled

with these mononuclear cells. It becomes a question, therefore, whether these cells are derived from the endothelium of the inflamed area, like those in the lymphatic gland, or whether they are brought to it by the blood stream.

Now in the case of the polynuclear leucocytes we are practically certain that they are brought by the blood stream, for it is found that they are increased in the blood and decreased in the organs in which they are produced, during septic inflammation

But in the case of the lymphocytes in chronic inflammatory processes, there is no such increase of them in the blood, their number, as compared with the polynuclear leucocytes, being normally very small, so they must either arise from a rapid division of the lymphocytes brought to the part by the blood stream, or be a local production of the cells, probably from the endothelium at the site of inflammation. This latter view is held by A. Whitfield, with whom I strongly agree. He looks on any endothelial or perithelial cell as capable of the production of mononuclear cells; in fact he holds that any connective tissue can become lymphoid tissue. This is only what is to be expected; viz., that a specialised cell, such as the endothelial cell, should revert to its simpler forms on rapid division.

Further, it is a well-known fact in surgery that after complete removal of glands new ones form,

and in cases of chronic inflammation new glands are found in unexpected places, such as in the muscles of the back, where we are taught by anatomists that there are no glands.

The conjunctiva seems to bear out this theory of origin of the lymphoid tissue from the endothelium most fully. The subepithelial tissue of the fornix, being richest in endothelium, through irritation during the first few weeks of life, becomes filled with lymphocytes and plasma cells, varying with the amount of stimulation; and, if further irritated by atropine, or if any form of chronic inflammation exist, it takes on the formation of typical lymphoid follicles, which are identical in structure and character with a small lymphatic gland and behave both in health and in disease in a similar way to those structures; further, in Parinaud's disease we have the association of follicular formation with glandular enlargement. Nothing to my mind can be stronger evidence than this of the local production of the lymphocytes and plasma cells.

The importance of the early formation of lymphoid tissue as a protection will be suggested in connection with infection in ophthalmia neonatorum and the action of silver nitrate as a prophylactic in that disease.

The lymphoid tissue appears first in the fornices and then spreads to the palpebral conjunctiva. It varies in extent with the amount of inflammation in the conjunctiva. Unless inflamed, the bulbar

conjunctiva contains no lymphoid tissue, and even then the mononuclear leucocytes disappear after the subsidence of the inflammation ; but even in this situation, follicles occur in cases of very chronic inflammation, such as in trachoma of the limbus. Plasma cells are always found in the lymphoid tissue, both in the conjunctiva and elsewhere, unless the tissue be diseased, as is the case in follicles infected with trachoma and tubercle, when the cells become rapidly broken up. They are less numerous in rapidly formed follicles and in new lymphoid tissue than in the older parts. They become increased in any tissue subjected to chronic irritation, and a notable instance of this is the bulbar conjunctiva when irritated by the friction of the trachoma granules, but they disappear at the foci of a disease affecting the tissue, as will be seen later on.

We now pass on to the histology of the follicular formation.

Follicular Formation.

So-called follicular conjunctivitis is characterised by the formation of follicles, which appear chiefly in the lower fornix. Occasionally in severe cases they are found in the upper fornix and on the tarsal conjunctiva. Their position in the lower fornix is a point of importance in distinguishing clinically this disease from trachoma, in which the follicles are principally situated in the upper fornix ; but

the presence of follicles on the upper lid is not absolutely diagnostic of trachoma.

True follicular formations, such as are so commonly seen amongst children, give rise to no symptoms and produce no change in the conjunctiva, disappearing spontaneously without leaving any trace behind; they can hardly, pathologically speaking, be called a disease, since microscopically they are seen to be identical in structure with the follicles found in the ordinary lymphatic gland, and show a marked difference in structure to that of a follicle infected with trachoma, except perhaps in the early stages, as will be described when treating of that disease.

Follicular conjunctivitis occurs in children at a time when all the adenoid tissues of the body are peculiarly active,[1] that is to say, when adenoids (which resemble very closely, both microscopically and pathologically, follicular conjunctivitis) and enlarged tonsils are found, and the lymphatic glands all over the body are apt to become enlarged on the slightest provocation.

Apart from children, these follicles also make their appearance in general diseases of lymphoïd tissue, as is sometimes seen in Hodgkin's disease. They also appear after the application of irritants to the conjunctiva, as in patients who suffer from atropine irritation.

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[1] Coppery, H., "*Conjunctivite folliculaire et végétations adenoides du naso-pharynx*," *Arch. d'Ophthal.*, 1899, xix., ii.

It is therefore seen that the follicle may arise (1) as the result of irritation, and (2) associated with general lymphatic enlargements. As a rule, both factors probably play an important part in follicular conjunctivitis. As we have already observed, the lymphoid tissue of the conjunctiva is of new formation. The follicles in an ordinary lymphatic gland, in which mononuclear cells evidently originate, in no way differ from those of follicular conjunctivitis, and I think, therefore, that these latter follicles may be looked upon as an effort on the part of the tissue towards the increased local production of mononuclear cells, either as the result of irritation or of general increase of the lymphoid tissue (pl. ii., fig. 1).

Histology.

The *epithelium* covering the follicles, although thrown into folds, does not dip down into the tissue beneath, as in trachoma. It is usually undergoing extensive mucoid change, and especially is this evident over the tops of the follicles. When this change is very excessive the epithelium is thinned, and the follicles which lie directly beneath the epithelium no doubt occasionally rupture through it, and subsequently become infected with pyogenic micro-organisms, which give rise to the discharge which is sometimes associated with this disease, and which, by producing further irritation, causes increased follicular formation.

PLATE II.

Fig. 1.—This section was made from a patient suffering from so-called follicular conjunctivitis, the source of irritation being a wart on the margin of the lower lid, which was rubbing over the surface of the cornea. A, Epithelium which is undergoing proliferation and mucoid change ; B, plasma cells beneath the epithelium ; C, endothelium of the follicle, which is deficient towards the surface ; D, an endofollicle well developed ; E, an early follicle, more highly magnified in fig. 2 ; F, plasma cells within the follicle, numbers of which are undergoing mitosis. (Pappenheim staining.) $\frac{1}{6}$ obj. No. 4 eyepiece.

Fig. 2.—An early endofollicle. This figure also shows the probable origin of the cells within the follicle (E, fig. 1). A, Endothelial lining ; B, proliferating endothelial cell ; C, transition cell between endothelial cell and mononuclear leucocyte ; D, mononuclear leucocyte ; E, plasma cell ; F, plasma cell undergoing mitosis ; G, transition cells between mononuclear leucocytes and plasma cells, or between endothelial cells and plasma cells. (Pappenheim staining.) $\frac{1}{12}$ obj. No. 4 eyepiece. Long tube.

PLATE 2.

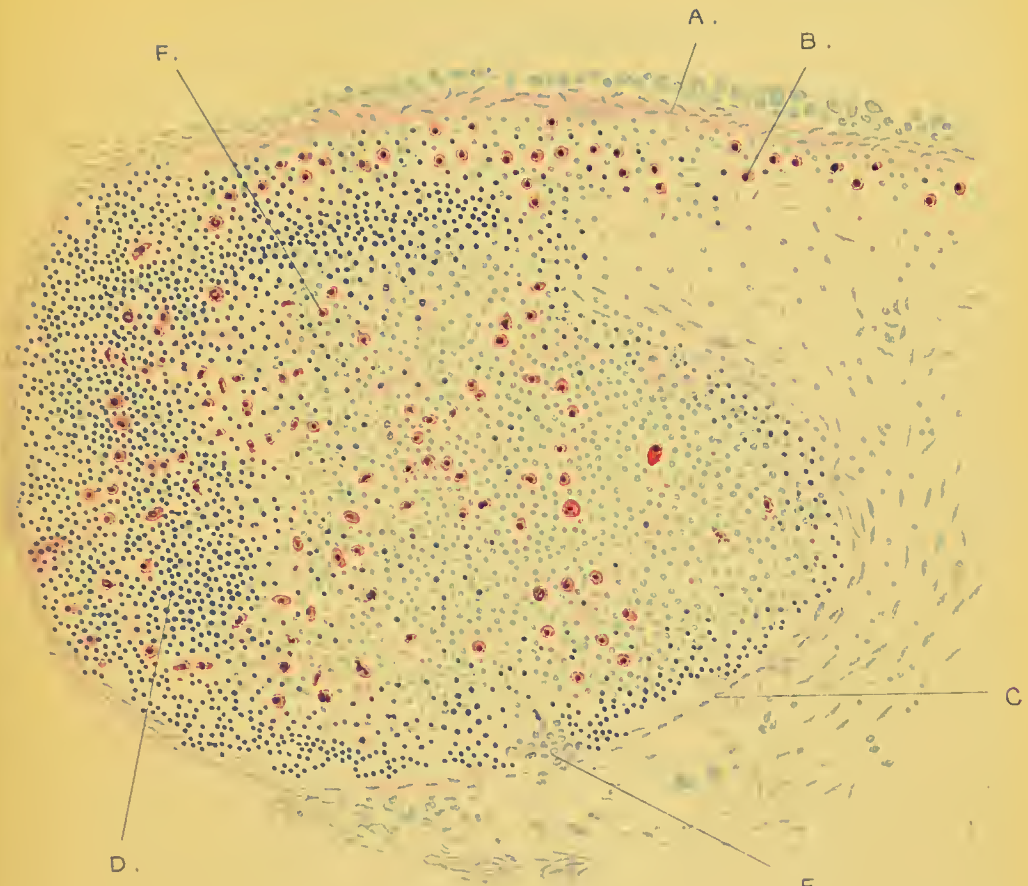

Fig. 1.

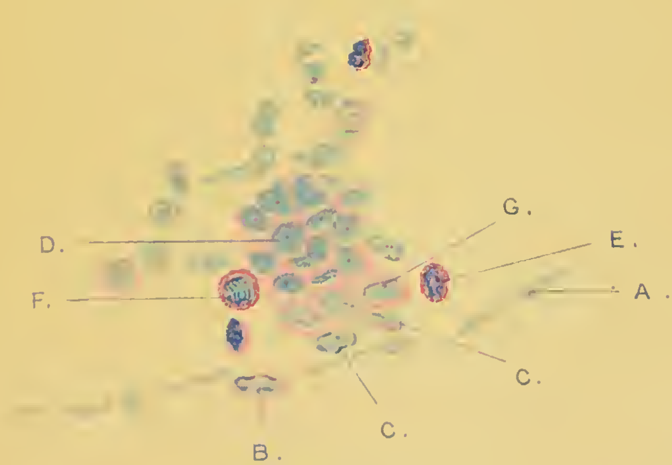

Fig. 2.

Bale & Danielsson Ltd lith.

The *Subepithelial Tissue.* — The follicles lie directly beneath the epithelium. They have sharply defined borders, and there is a band of lymphoid tissue directly beneath the epithelium, connecting one follicle with another. This lymphoid tissue in the neighbourhood of the follicles often contains a large number of plasma cells. The deeper layers

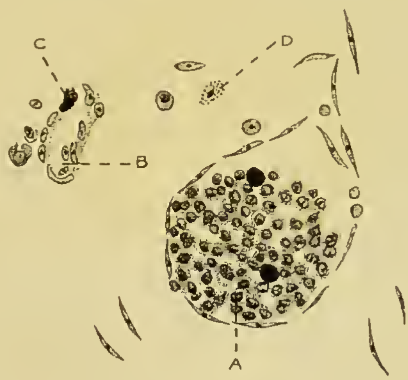

FIG. 31.—Small vein and artery from the deep layer of connective tissue. A, Vein containing large numbers of mononuclear leucocytes and a few plasma cells; B, small artery; C, mitosis of an endothelial cell; D, mast cell. (Pappenheim staining.) $\frac{1}{12}$ obj. No. 2 eyepiece.

of the conjunctiva are unaltered, there being comparatively no increase in the cellular elements or proliferation of the connective tissue cells, even in the cells in close proximity to the follicles. Occasionally lymphatics, and in some instances small veins, are found packed with mononuclear leucocytes and plasma cells (fig. 31).

The Follicles.—The follicles may be single, or, as occurs when they are older and larger, they may

contain masses of darkly staining cells which are due to the presence of another younger follicle within, thus resembling a lymphatic gland. They consist of a definite outer wall of endothelial cells, which are often found proliferating. This outer wall is absent where the follicle is connected with the band of lymphoid tissue beneath the epithelium. Within the outer capsule of endothelium is a very delicate stroma, best seen in the older follicles. In this stroma are found occasional blood-vessels, also vessels which resemble lymphatics, since they are never found containing blood.

The *cells of the stroma* consist of three types :—

The *first form of cell* making up the stroma is a typical endothelial cell. Some of these cells undergo a change, attention to which was first drawn by Leber. In connection with trachoma, he described these cells as containing "half-moon shape," and large "coccoid-like" bodies, which he at first thought were parasites. Now if these cell inclusions be carefully examined, the "half-moon shaped bodies" are seen to be not really half-moon shaped at all, but round ; that is to say, the chromatin—which is that which takes up the stain —is chiefly situated on one side of a round body, giving a half-moon shaped appearance. Numbers of the larger "coccoid-like bodies" show a pale centre with a darkly staining outer rim of protoplasm (pl i., fig. M N).

Now these endothelial cells often also contain

within them fully formed lymphocytes. The "coccoid and half-moon shaped bodies" are evidently produced by the digestion of the lymphocytes by the endothelial cells, all stages in the process being observable; they are not only found within the endothelial cells, but also within the giant cells. As the cell inclusion is digested the protoplasm of the endothelial cell becomes vacuolated around it, and when completely digested nothing but a vacuole is left. During the process of digestion the inclusion becomes more darkly staining, due no doubt to the shrinking and matting together of the reticulum of the cell.

In a like manner, whole plasma cells can be found within these endothelial phagocytes, the protoplasm of the endothelial cells around them becoming vacuolated, until only the nucleus remains as a coccoid or half-moon shaped body. This endothelial phagocytosis takes place to an enormous extent in "resolving" follicles, after the subsidence of inflammation, and no doubt accounts very largely for the disappearance of the mononuclear infiltration after all inflammatory exudations.

That this process of digestion of cells takes place in the endothelial cells elsewhere in the body (peritoneal cavity) has been shown to me by Briscoe (see also "The Origin of the Complement in the Peritoneal Cavity," *Orth. Festschrift*, 1903), some drawings from whose films I have made. They were taken from the peritoneal cavity

of a guinea-pig two days after the injection of its own blood, and show the inclusion of poly-nuclear leucocytes (pseudo-eosinophiles) by the endothelial cells and the process of their digestion. A similar change can also be seen in the endothelial cells on Descemet's membrane in cases of keratitis punctata.

The *second form* of cells making up the stroma are more typical connective tissue cells with the ordinary pale blue nucleus, red nucleolus and badly staining protoplasm, when stained by Pappenheim's method. This cell is extremely rare in the follicles of follicular conjunctivitis.

The Third Form of Cell.—Clasmatocytes or wandering endothelial cells are large cells; their nucleus stains pale blue with one or two red nucleoli, the cytoplasm staining red with Pappenheim. These cells are intermediate in structure between the endothelial cells and the plasma cells, and cells are always found of which it is impossible to say whether they are clasmatocytes or plasma cells (pl. i., fig. K).

The Cells of the Follicles.—The character of the cells varies somewhat with the age of the follicle. In young follicles they consist very largely of mononuclear leucocytes (mainly lymphocytes) with a few scattered plasma cells. All the cells take the stain well; none of them show any signs of degeneration, and many can be found undergoing mitosis.

In the larger and older follicles the cells, although consisting largely of lymphocytes, contain increased numbers of clasmatocytes and well-formed plasma cells. In some of the older follicles, as has already been mentioned, there are found collections of darkly staining cells with lighter centres, which are strongly suggestive of the commencing formation of new follicles inside the old (endofollicles). These groups are found in their early stages at the periphery of the follicle; some of the endothelial cells of the lining in their neighbourhood are proliferating, which probably furnishes their origin.

The differential diagnosis between this disease and trachoma will be dealt with under that disease.

Lymphoma of the Conjunctiva.

The so-called lymphoma of the conjunctiva has clinically the appearance of a very large follicle; it gives rise to no trouble, attention usually being drawn to it by some slight conjunctivitis, or it may be discovered accidentally.

The most common situation for lymphoma is the inner end of the lower fornix. I have made sections from one such case, in a girl aged 25, who some weeks previously had had a mild attack of Koch-Week's conjunctivitis (fig. 32).

HISTOLOGY.

The *epithelium* over the surface had undergone some mucoid change.

The Subepithelial Tissue.—The lymphoma consists of a mass of encapsuled lymphoid tissue. Directly beneath the epithelium, and therefore in the neighbourhood of the small vessels, there is

FIG. 32.—Lymphoma of the conjunctiva. A, Epithelium, which at one point is slightly torn; B, subepithelial tissue of normal conjunctiva; C, lymphoma containing large numbers of endofollicles; D, deep layer of the subepithelial tissue of the conjunctiva; E, small vessels packed with mononuclear leucocytes and plasma cells; F, endothelial lining of the lymphoma; G, large endofollicle; H, smaller endofollicles, many of which are encapsuled by endothelium; J, giant cells. ⅔ obj. No. 2 eyepiece.

a layer of plasma cells. The lymphoid tissue is arranged in an exactly similar manner to that of a lymphatic gland. The stroma and the lining membrane of the lymphoma consist of endothelium and blood-vessels, numbers of the small veins of which are packed with mononuclear

leucocytes and plasma cells. Within this stroma there are large numbers of typical follicles, consisting of mononuclear leucocytes and plasma cells. These follicles, at least in their early stage, are always found originating either from the endothelial lining of the lymphoma or from the blood-vessels within. The follicles contain, in addition to the lymphocytes and plasma cells, endothelial phagocytic cells and giant cells.

Conclusions.—In lymphoma, which is the outcome of previous inflammation, therefore, we have the connecting link between the so-called follicle of follicular conjunctivitis and an ordinary lymphatic gland, the lymphoma being in size, structure, and probably in function, identical with an ordinary small lymphatic gland.

The Discharge.

The discharge varies with the form of conjunctivitis.

In the *purulent forms* it is mainly serous in the early stages, and contains a gradually increasing number of polynuclear neutrophiles with a few scattered mononuclear cells. After the first twenty-four hours the discharge becomes typical muco-pus.

With a view of ascertaining the relative proportion of cells in the discharge I examined twenty cases of Koch-Week's conjunctivitis in their early purulent stage by smear preparations stained with Jenner blood stain. In counting, only

well-formed cells whose character could easily be told were taken. In telling the degenerative forms, difficulty arose between varieties of mononuclear cells.

Polynuclear leucocytes (neutrophiles) represent 94 per cent. of the cells in the discharge. It is these cells which are the great phagocytes; they were often found containing Koch-Week's bacillus in large numbers, some of them becoming vacuolated and some swelling up until the cell consisted of nothing but a cell wall with the nucleus on one side of it. In those cells which have undergone extensive vacuolation the organisms are usually not seen, having probably undergone the process of digestion.

Another kind of degeneration often seen is shown by the whole cell staining faintly with the dye, being evidently dead. The nuclei are homogeneous and show no chromatin fibres (hypochromatosis), and the protoplasm of the cell becomes, if anything, rather more granular (pyknosis). The whole cell may increase in size and burst, with the result that the nuclei are separated and the protoplasm of the cell scattered, whilst the cell wall sometimes remains as a small rounded mass.

Large mononuclear cells make up about 3 per cent. of the discharge. It is difficult to distinguish some of the small or lymphocytic cells, in their extreme stages of degeneration when only the nucleus remains, from lymphocytes when the proto-

plasm is lost in process of degeneration, unless some of the protoplasm is still adherent. The whole cell stains faintly, the nuclei show large pale granules, the cell is increased in size, and is sometimes found burst, with extrusion of its contents. Occasionally one finds the protoplasm much vacuolated.

Small mononuclear cells (lymphocytes) make up about 3 per cent. of the discharge, but their number is increased towards the end of a case. It is as a rule impossible, as has been pointed out, to make a differential count between the large and the small varieties, as in the degeneration stages they resemble each other. It has been shown recently that these cells are feebly amœboid, but I was unable to find any containing organisms. In the process of degeneration they swell up, becoming very irregular in shape, and have the appearance of being filled with coarse, faintly staining granules, which subsequently disappear.

Eosinophiles and Basophiles.—In examining the discharge from the twenty cases mentioned above, I found only one typical eosinophile and one basophile (mast cell), so that it may be assumed that their appearance is rare.

In the *non-purulent forms* of conjunctivitis, such as that due to the Morax-Axenfeld bacillus, the discharge is a soapy secretion found on the lid margins, which consists almost entirely of epithelial *débris* with Meibomian secretion and bacilli. There are a few scattered polynuclear cells, which

are probably due to the presence of other pyogenic organisms in the conjunctival sac, and not to the diplobacillus, which is non-pyogenic.

With the view of demonstrating the presence of other cell elements, more especially epithelial, plasma, and mast cells, I have stained with Pappenheim's plasma stain the discharge from a number of cases of gonorrhœal, Koch-Week's, and diplobacillary conjunctivitis, and of trachoma. This stain is also by far the most satisfactory for the staining of organisms which do not retain the stain by Gram's method, such as gonococci, Koch-Week's bacilli, and diplobacilli.

Epithelial cells were found in all cases, often containing organisms, being in the greatest proportion in diplobacillary conjunctivitis, the discharge from which contains little else but these cells and the organism.

Plasma Cells.—Plasma cells are found in large numbers in trachoma, and are best obtained by gently rubbing the cover-glass over the surface of the lid. Every field contains two or three well-formed cells. Follicular conjunctivitis also shows a considerable number of these cells, but they are not present to nearly the same extent as in trachoma—a point which may prove to be of assistance in making a differential diagnosis. They are also found in acute conjunctivitis, towards the end of the case, but are comparatively few in number, only two or three being found in each

smear preparation ; that is to say, the more acute the case the less the number of plasma cells found. As will be seen, these cells very rapidly become broken up in the presence of an organism, therefore, in inflammatory diseases in which the organism is present in the epithelium these cells do not occur in any extent in the discharge, especially as their amœboid movements seem to be very slight. Like the other cells these cells undergo hypochromatosis and pyknosis, the latter form of degeneration being most common. I have never been able to find organisms in these cells.

Mast Cells (Basophile).—Mast cells are very rare in acute conjunctivitis, and only one undoubted cell was found in the smear preparations from those cases. In trachoma these cells are not infrequently found, being more plentiful in long-standing cases ; they are also found in the discharge from phlyctenulæ.

Polynuclear Eosinophiles.—In all inflammations of the conjunctiva these cells are occasionally found in the discharge, but are especially abundant in some forms, such as pemphigus and vernal catarrh. Associated with the clinical condition of the latter disease they seem to be diagnostic, as has been shown by Herbert. In one case of conjunctivitis, probably due to the sting of some insect, I have found large numbers of these cells. They are best demonstrated by staining with Jenner's, Ehrlich's triacid, or by Leishman's stain, the latter being

the most satisfactory, as it can be used for the tissues also.

Conclusions as to the cells of the discharge. It may be said that in all the acute forms of conjunctivitis the discharge is principally made up of polymorphonuclear neutrophiles (94 per cent.), with an occasional polymorphonuclear eosinophile, but in some diseases, such as pemphigus and vernal catarrh, the numbers of the latter cell may be largely increased. In the chronic forms of conjunctivitis, especially when the disease affects chiefly the subepithelial tissue, as in trachoma, plasma cells are found in large numbers ; they are also occasionally found in very small numbers in the discharge from acute conjunctivitis.

Mast cells are found in the discharge principally in diseases of the subepithelial tissue, such as trachoma and phlyctenulæ, but they are also occasionally found in the more acute forms of conjunctivitis, when of long standing.

The cells undergo degeneration by—

(1) Vacuolisation, which seems generally to be due to the digestion of organisms, &c.

(2) Hypochromatosis—gradual fading of the cell, due to the absorption of fluid.

(3) Pyknosis—shrinking of the protoplasm of the cell, due to the loss of fluid. The latter two forms of degeneration depend on the osmotic properties of the cell wall.

Contagious Conjunctivitis due to Micro-organisms.

Gonorrhœal Conjunctivitis.

Clinically the disease is usually divided into two forms:—

(1) That found in newborn infants.

(2) That attacking adults.

Although the organism is identical in the two forms the results differ somewhat, owing to the varying conditions of the conjunctival tissue at birth and in the adult.

Newborn Infants (ophthalmia neonatorum).—The first point to emphasise is that all cases of ophthalmia neonatorum are not gonorrhœal, although, indeed, the latter amount to about 70 per cent. of the total number of cases.

The incubation period varies from two to three days, or even longer. According to Piringer the length of time of incubation seems to have a definite relation to the severity of the attack, it being more acute the shorter the incubation period. The length of the incubation period is also of importance in deciding whether the infection took place at the time of birth, through the omission by the accoucheur of such precautions as Credé's method, or secondarily from the clothing, &c., of the mother, due to careless nursing.

Newborn children are especially prone to infection of the conjunctival sac with micro-organisms,

as has been previously shown, for the following reasons:—

Firstly, the absence of lachrymal secretion.

Secondly, the epithelium is not so thick, and there is no flattened layer as in the adult. Numbers of the cells, especially in the fornix, have been lost, owing to mucoid change, which in places leaves the basement membrane bare.

Thirdly, there is an absence of leucocytes from the lymphoid tissue.

Fourthly, although the eyelids, no doubt, are closed as the child passes through the vagina, they are in contact with the secretion for some hours before birth.

Histology.

The following observations were made on three cases of ophthalmia neonatorum (fig. 33). They were all extremely severe cases; one had ended in complete destruction of both eyes, and the other two of one eye each. The tissue was removed from the lower fornix in two of the cases, and from the upper fornix in one, during the third week of the disease. The tissue was hardened in alcohol, embedded in paraffin, and cut both vertically and parallel to the surface.

The *epithelium* on the surface is somewhat irregular in thickness and is desquamating, some of the superficial cells containing the gonococcus. The conjunctiva becomes papillated in consequence

of the swelling beneath. This is best seen in sections cut parallel to the surface, when papillæ containing numerous blood-vessels are seen completely surrounded by epithelium.

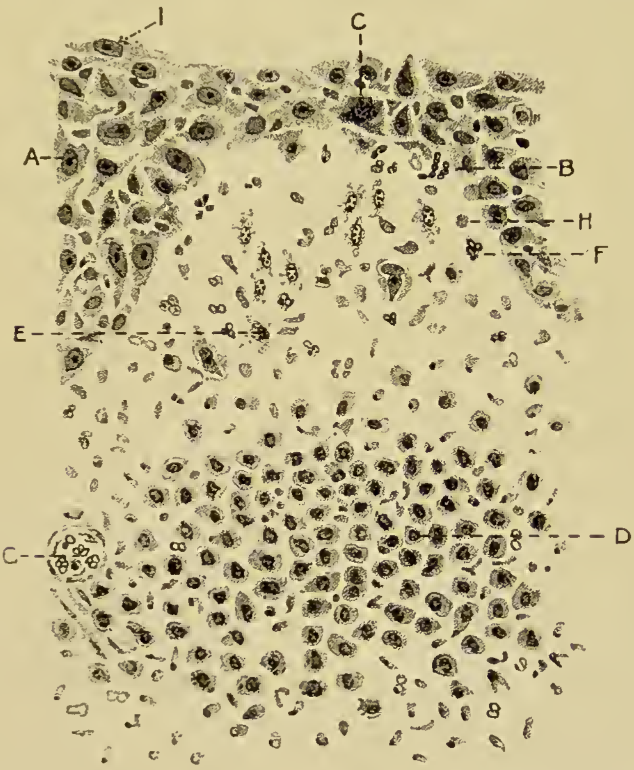

FIG. 33.—Gonorrhœal conjunctivitis, showing the distribution of plasma cells, &c. A, Epithelium with papilla, the cells of which are much separated by the passage of enormous numbers of polynuclear leucocytes; B, polynuclear and mononuclear leucocytes in the epithelium; C, mitosis in an epithelial cell; D, plasma cells; E, degenerating plasma cells as they approach the epithelium; F, polynuclear leucocytes; G, new blood-vessel with proliferating endothelium; H, mononuclear leucocytes, most of which are degenerating; I, gonococcus in an epithelial cell. (Pappenheim staining.) $\frac{1}{12}$ obj. No. 4 eyepiece.

The epithelial cells are much separated from each other, chiefly, no doubt, by the passage through them of enormous numbers of polynuclear leuco-

cytes, since the conjunctival sac will often become filled with pus in less than five minutes after cleansing. Many of the cells show evidence of mitosis.

Between the epithelial cells are found numbers of mononuclear and polynuclear leucocytes, and although in the section the greater number seen are mononuclear cells, the polynuclear cells are found in greater numbers in the discharge, doubtless due to the greater power of amœboid movements on the part of the latter cells.

The Subepithelial Tissue.—There is an extensive exudation into the superficial layer of connective tissue; the vessels in the deeper layer of connective tissue are dilated, and in and around the papillæ there are quantities of small vessels of new formation with proliferating endothelium; these vessels contain large numbers of polynuclear leucocytes and show many beautiful examples of diapedesis. The connective tissue cells of the superficial layer are proliferating, but not to any marked extent. The cells in the deeper layer of connective tissue show practically no changes.

The Cells of the Exudation (*Polynuclear leucocytes*).—Although these cells are found in large numbers in the subepithelial tissue they are not nearly so numerous as the mononuclear cells; their relative proportion becomes increased in the epithelium, and in the discharge they make up about 94 per cent. of the cells. Hence it is seen that

although they make up the greater proportion of the cells of the discharge, they are not seen in such enormous numbers in the subepithelial tissue when compared to the mononuclear cells—a fact which can easily be accounted for by their more active amœboid movements. Probably, except under special circumstances, these cells never re-enter the circulation.

Mononuclear Cells. — Mononuclear leucocytes, both large and small, are found in great numbers scattered throughout the exudation, and are seen best in the papillæ, which contain little else but these cells, many of which are degenerating, together with a few endothelial cells and new blood-vessels.

Plasma Cells.—Of great interest is the distribution of the plasma cells in this disease. They are found in great numbers in the connective tissue beneath the papillæ, but where they approach the epithelium they become rapidly broken up, the cells staining more faintly and losing their protoplasm ; hence they are practically absent from the papillæ, no doubt owing to the presence of the toxin produced by the gonococcus growing in the epithelium. The fact that the plasma cells become broken up is of great importance in showing the action of some powerful toxin on the cells, and as will be seen in dealing with trachoma, this fact is of great use in demonstrating the existence of a disease in which the cause has not been discovered. I have been unable

to obtain a specimen showing the early stages of this disease.

Koch-Week's Conjunctivitis.

Bacteriology.—The bacillus of this disease is one of the most common causes of purulent ophthalmia, being found all over the world. The disease occurs frequently both in adults and in children, in sporadic and epidemic forms, often running through a whole school, as it is extremely infectious. Morax found 125 cases out of 1,430 general ophthalmic out-patients. Weeks, Kartulis, and Hoffmann have also pointed out that it occurs in epidemic form.

It almost invariably affects both eyes and is characterised clinically by intense injection of both palpebral and ocular conjunctivæ. The injection in the ocular conjunctiva is very marked and there are numerous hæmorrhages all over the surface. At the same time it is entirely free from chemosis.

I have examined thirty children with this typical clinical condition and have found the bacillus in twenty-five cases, generally unassociated with any other bacteria. In five out of the twenty-five cases above mentioned it was associated on the culture media with the *Staphylococcus albus*, pseudo-diphtheritic, and diplo-bacilli. From these observations, together with the examination of a large number of cases by smear preparations, I think it is possible to say, almost with certainty, from the

clinical condition, whether a case is due to this organism or not. Towards the end of the attack follicles form in the fornix which persist for some time after the disease has subsided. Hoffmann and Markus have also pointed out the frequency of phlyctenulæ associated with this disease.

Histology of Koch-Week's Conjunctivitis.

I have had the opportunity of examining the conjunctiva removed from the lower fornix at its junction with the ocular conjunctiva in two cases. The first was from a severe case of the disease on the second day, in a girl aged 20, whilst the second was from a mild case on the eighth day of the disease, in a man aged 30. I have also examined a number of specimens from the lower fornix showing follicular formations; these follicles usually begin to appear about the sixth day of the disease, forming rather earlier in children, and persist for some time after the disease subsides.

The Epithelium.—The epithelium shows extensive mucoid change, which is not distributed evenly throughout, but occurs in patches over the area of exudation into the subepithelial tissue, and is more marked in the case of long standing than in the early case; the epithelium is occasionally found dipping down into the subepithelial tissue.

The Subepithelial Tissue.—The exudation, unlike gonorrhœal conjunctivitis, is unevenly distributed

throughout the subepithelial tissue, which contains, between the patches of exudation, very few more cellular elements than the normal number. In the areas of exudation in the subepithelial tissue the vessels are dilated and the endothelium proliferating, and there are quantities of newly formed vessels which show as well-marked areas in the sections from the case of two days' duration ; there are also numerous small hæmorrhages into the subepithelial tissue. The character of the cellular exudation varies in the two cases.

In the *early case* the exudation consists largely of polynuclear leucocytes, but there are also numbers of mononuclear cells, which are principally lymphocytes, together with a few plasma cells. These cells are found around the blood-vessels of both the superficial and deeper layers, the polynuclear leucocytes (spider cells) being more numerous around the small newly formed vessels, whilst the mononuclear varieties are found around the larger vessels : there are very few plasma cells present.

In the *older case* there are more newly formed blood-vessels, the mononuclear exudation is more marked, and there are fewer polynuclear leucocytes than in the early case. Plasma cells are present in large quantities in the situations of the mononuclear exudation, that is to say, around the vessels ; they are broken up wherever there are large numbers of polynuclear leucocytes, that is to say, at the site of most active inflammation. The follicular formations

do not differ in structure from those described under follicular conjunctivitis. In the early stages of their formation they do not contain many plasma cells, these cells gradually increasing in number as the attack subsides. As the follicles begin to disappear the endothelial phagocytic cells make their appearance in enormous numbers, and I have been able to count as many as twelve in a single field of a $\frac{1}{12}$ objective.

From the above observations it is seen that in the early stages the plasma cell is not present to any extent, but that as the disease subsides and the tissues become locally immune it appears in increasing numbers. Evidently the affection of the subepithelial tissue is much more localised than in gonorrhœal conjunctivitis, as evidenced by the unequal distribution of the exudation, but at the same time it is very acute, as shown by the multiple hæmorrhages and polynuclear exudation. This localised infection no doubt accounts for the frequency of phlyctenules and the localised hæmorrhages seen in the bulbar conjunctiva in this disease, and also no doubt for the frequency of follicular formation after the acute stages have subsided.

Histology of Diplobacillary Conjunctivitis.

W. Stock has examined a whole conjunctival sac from a patient who died while suffering from a chronic diplobacillary conjunctivitis. I have

examined pieces of tissue removed from the lower conjunctival sac in three typical cases of two, three and four weeks' duration. Although my observations are in the main similar to his, he does not demonstrate the character of the cells by means of cytoplasmic stains.

The Epithelium.—The greatest changes take place in the epithelium, which undergoes very extensive desquamation and mucoid degeneration. In the latter stages of the disease it dips down into the subepithelial tissue and new glands are formed; these new glands are very liable to become occluded, with the result that retention cysts are produced.

The Subepithelial Tissue.—There is no increase in the polynuclear or mononuclear leucocytes in the subepithelial tissue, except in the regions where the epithelium dips down into it, or where there are cystic formations. Elsewhere the change consists in a large increase in the number of plasma cells, of which the exudation almost entirely consists; directly beneath the epithelium the cells are somewhat broken up, no doubt owing to the presence of the toxin. There is also a considerable increase in the mast cells of the underlying tissue. In one case, which was of long standing, there was a considerable amount of hyalin degeneration present.

The diplobacillus is a non-pyogenic organism, and causes a conjunctivitis which is extremely

chronic if untreated, but very amenable to treatment in the early stages.

It produces the greatest changes in the epithelium in which it grows. The reaction caused by the toxin in the subepithelial tissue is not an exudation of polynuclear or mononuclear leucocytes, as is seen in the more acute forms, such as Koch-Week's and gonorrhœal conjunctivitis, but is the production of plasma cells. These cells, as they come near the epithelium, are broken up through the presence of the bacilli, and therefore, owing probably to the low vitality of these cells, the disease is not eradicated spontaneously.

LECTURE III.

Trachoma.

Trachoma, I think, is a specific infective disease of the subepithelial lymphoid tissue of the conjunctiva, characterised by the formation of follicles and by infiltration, which go on to subsequent cicatrisation and partial obliteration of the conjunctival sac.

This disease has been known since the days of Celsus, but it is only during the last century that it has attracted much attention, it being then realised that whole armies, schools, &c., were affected with the disease, and that the sufferers, being sent to their homes, spread the infection broadcast.

At the present time the disease does not seem to be so acute as the form of it described in earlier days, except perhaps the type which still exists in Egypt and in some countries of the East.

The patient's attention is usually drawn to it either by a slight discharge, photophobia, or drooping of the lid, the subjective symptoms in the early stages often being very slight. Later on, attention may be drawn to it by the failure of vision caused by pannus.

Piringer has proved beyond all doubt, by inoculating one patient with discharge from another, that the disease is directly contagious, and further, by his inoculation experiments, he has proved that all the clinical forms of the disease are identical, as he produced various forms of it by inoculating the discharge from one case into different patients.

Clinically, the disease usually appears at first in the upper fornix and is characterised by the formation of follicles. These follicles may remain for a long time and reach a large size without giving rise to any symptoms. At other times a muco-purulent discharge is set up. This muco-purulent discharge does not occur in all cases, or at the same period of any particular case, and indeed may not occur at all throughout a case. Pyogenic organisms are always found in the discharge ; and indeed I think the purulent discharge in these cases may be looked upon as a septic infection of the conjunctiva in addition to the trachoma, which without doubt lowers the vitality of the tissue and provides a means of entrance to the organisms by rupture of the follicles. This muco-purulent conjunctivitis may have varying effects on the disease. It may be associated with increased spread, as is seen in the most virulent cases, which are usually accompanied by a quantity of discharge ; or it may bring about its cure, the reasons for which will be discussed more fully when speaking of its pathology. Not only are

follicles formed in the subepithelial tissue, but diffuse infiltration of the tissue occurs, the conjunctiva appearing red, brawny and swollen. Although, pathologically speaking, follicular formations and infiltration do not occur apart, they receive names to distinguish them clinically in this disease. Hence the terms follicular, papillary, in which the infiltration is chiefly superficial; brawny œdema (Stelwag), in which deep infiltration is broken up by fibrous tissue.

The etiology of pannus will be discussed with its histology.

Histology.

These observations were made on sections from over thirty cases of trachoma.

The Epithelium.—In the earliest stage of all the epithelium shows little change, but directly any discharge appears the epithelium becomes infiltrated with leucocytes. These leucocytes, unlike those of the deeper layer of tissue, are largely of the polynuclear variety; and no doubt their presence is due to pyogenic organisms growing in the epithelium, since without infection they do not usually appear in any number in the early stages of the disease. The epithelial cells undergo increased mucoid change over the tops of the follicles, and the epithelium at times becomes almost lost (pl. iii., fig. 1). In the crypts between the follicles and in the folds produced by the swelling of the sub-

epithelial tissue the epithelium is undergoing extensive mucoid change, giving the appearance of new gland formation. Actual downgrowths of the epithelium also occur in the form of papillæ, which may subsequently undergo mucoid change with the formation of new glands, as has been described under the general effects of inflammation on the epithelium. Keratinisation of the epithelium may take place if there is any deficiency in lachrymal secretion, mucoid change in the epithelium being thereby prevented. (*See* Secondary Xerosis.) This is specially liable to occur on the prominences produced by scar tissue.

Subepithelial Tissue.—In the subepithelial tissue the changes are of two main types:—

(1) Infiltration.

(2) The formation of follicles.

They always occur together, but one may be in excess of the other, producing the different clinical conditions previously described.

(1) *Infiltration.*—Trachoma, unlike follicular conjunctivitis, is by no means limited to the layer lying directly beneath the epithelium, but spreads to the deeper layers of the tissue of the conjunctiva involved.

Situated directly beneath the epithelium and between the newly formed papillæ are solid masses of plasma cells (pl. iii., fig. 1). Comparatively few of these cells are found between the epithelial cells of the surface, but for all that they are found

PLATE III.

FIG. 1.—A fully-formed follicle infected with trachoma. A, Epithelium with papilla-like processes; B, epithelium becoming thinned over the surface of the follicle; C, papilla packed with plasma cells; D, degenerating plasma cells; E, blood-vessel; F, infiltration of subepithelial tissue; G, outer "radzone" of mononuclear leucocytes (mainly lymphocytes); H, epithelioid-like cells (degenerating leucocytes); I, large mononuclear leucocytes; J, endothelial cell containing the coccoid bodies of Leber (clasmatocyte); K, vessel with proliferating endothelium, with a plasma cell in its neighbourhood; L, central area of broken-down leucocytes; M, hyaline material; N, connective tissue cell.

FIG. 2.—Trachoma (Stelwag's brawny œdema) showing the necrosis of the plasma cells in the infiltration. A, Plasma cell; B. plasma cell breaking up; C, hyaline material due to the breaking up of the cells; D, fibrous tissue, staining slightly on account of the presence of hyaline; E, young connective tissue fibre. (Pappenheim staining.) $\frac{1}{12}$ obj. No. 4 eyepiece.

PLATE 3.

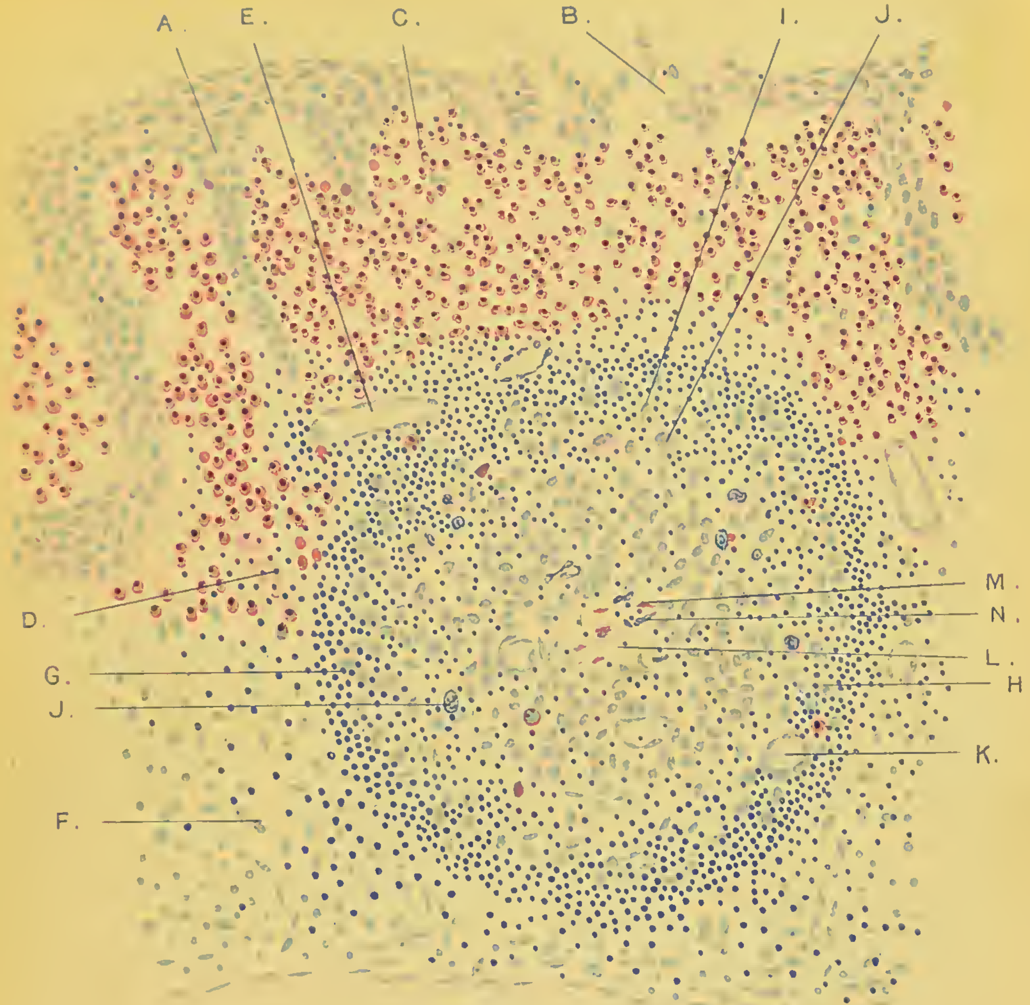

Fig. 1.

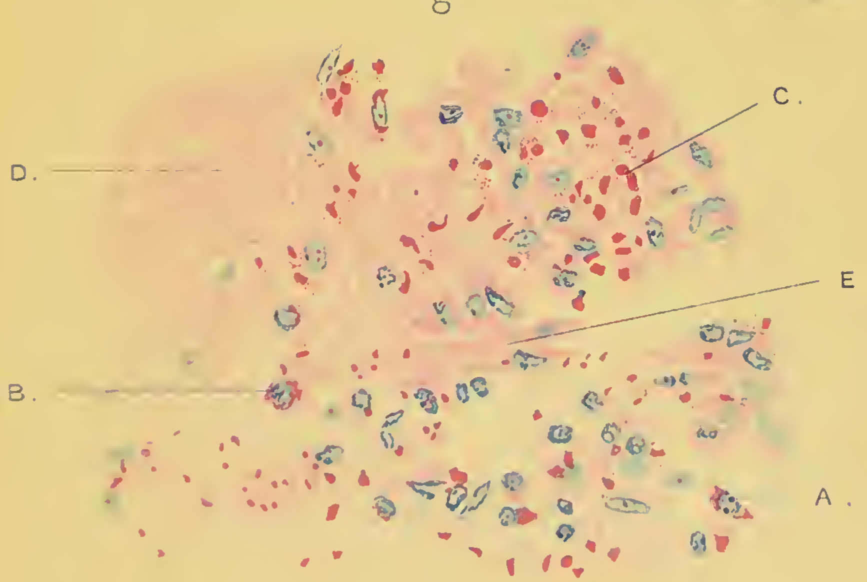

Fig. 2.

Bale & Danielsson L^td lith

in numbers in the discharge ; no doubt many of them make their way through broken surfaces, and indeed, the best way to obtain these cells in the discharge is by rubbing a cover-glass over the surface of the palpebral conjunctiva.

In this layer of cells are also found a number of new blood-vessels, the endothelial cells of which are undergoing active proliferation. The infiltration, indeed, consists chiefly of lymphocytes, together with a few large proliferating endothelial cells (clasmatocytes). There are also a few scattered plasma cells, most of which are undergoing disintegration. Deeper still and extending up into the layer already described, and around the follicles in long-standing cases, is a quantity of dense fibrous tissue, which is extremely rich in mast cells.

(2) *The Follicles.*—The follicles differ considerably in structure from the healthy follicles found in the lymphatic glands and in follicular conjunctivitis. They are usually found in the lymphoid layer, but may be more deeply situated, and their structure varies with their age. The cells of which they are composed, at any rate towards the centre, can rarely be found undergoing mitosis.

A newly infected follicle in trachoma resembles closely a new follicle in follicular conjunctivitis, but can usually be distinguished from it if carefully examined. There is a single layer of somewhat elongated flattened cells, which appear more

or less to line the follicle and to be of endothelial origin, but the continuity of these is much more broken up than in follicular conjunctivitis. Inside this lining an ill-defined reticulum can be made out between the cells, which consist first of an outer layer, chiefly of darkly staining lymphocytes. Towards the centre of the follicle are found a number of other cells slightly larger, but paler in their staining reaction, which is suggestive of degenerative changes having taken place in them. These cells are probably derived from the outer layer by degeneration, due to the action of the disease, and may be described as epithelioid-like cells. Scattered in this central area are a few large endothelial cells, both of the clasmatocytic and phagocytic varieties.

It is very rare to find well-formed plasma cells within the trachomatous follicle, as when they appear they seem rapidly to degenerate.

The Older Follicles.—(Pl. iii., fig. 1) An older follicle consists of a capsule of connective tissue which is considerably infiltrated with lymphocytes, especially if the disease be spreading. As a rule no definite endothelial lining can be made out. The connective tissue cells are mostly well formed, and a number are usually found proliferating. This tissue contains a number of mast cells. The amount of stroma varies considerably with the age of the follicle, but it is only in the old degenerated follicles that it is at all apparent. It consists at

first of very fine processes, which are the branches of true connective tissue cells, often embracing one or two lymphocytes, and best seen in the centre of an old follicle where most of the constituents have degenerated.

The other type of stroma cell, which is an endothelial cell, is large, with a pale blue nucleus and protoplasm, often containing the coccoid or half-moon shaped bodies described by Leber, which have been treated of under follicular conjunctivitis. Numerous blood-vessels are found within the older follicles, with proliferating endothelium, the vessels being situated towards the periphery of the follicle and gradually spreading towards the centre as the follicle becomes organised.

The *cells composing the older follicles* consist of an outer layer of darkly staining lymphocytes. Inside this, again, the cells are found mixed with others, more faintly staining and somewhat larger (epithelioid-like cells). In this layer and the next are a number of large clasmatocytes, which towards the centre show well-marked signs of degeneration, the nucleus becoming pale and staining faintly, whilst the cytoplasm disintegrates and can be found free in the centre of the follicle. Sometimes rounded masses of hyaline material are found which appear to be derived from the broken-up cytoplasm of these cells, since they have much the same staining reaction.

Plasma cells are to all intents and purposes absent

from the follicle, although they are occasionally found in the outer zones and in the neighbourhood of the vessels. They seem to disintegrate very quickly.

None of the cells, at any rate towards the centre of the follicle, can be found undergoing mitosis.

The future life-history of a follicle varies after reaching the stage above described. It may result in—

(1) Extrusion.

(2) Organisation.

Extrusion of the follicle may occur—

(*a*) As the result of operation.

(*b*) From cicatricial contraction.

(*c*) As a consequence of septic infection.

(*a*) The late results of extrusion of the follicle are best seen in sections made from the conjunctiva after expression has been performed. I have sections from severe cases of trachoma which show both the early and late stages, after the operation.

In sections of the early stage the thick fibrous wall of the follicle encloses a space which communicates with the surface of the conjunctiva, the epithelium of which has been ruptured. The wall of the follicle and the epithelium in the neighbourhood of the rupture are infiltrated with polynuclear leucocytes (spider cells), no doubt owing to the presence of septic organisms. Within the follicle there remain a number of blood corpuscles, mononuclear leucocytes, plasma cells, &c.

In sections from the older cases the polynuclear leucocytes are still present, both within the follicle and in its wall. Fine strands of connective tissue cells have made their way from one wall to the

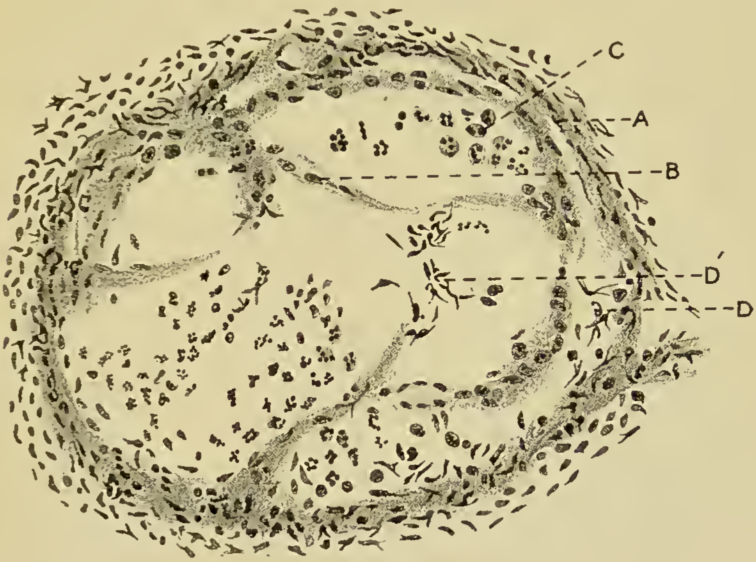

FIG. 34.—A follicle one week after expression. The opening on to the surface is not shown, but is seen in many of the sections. A, fibrous tissue wall; B, proliferating strands of connective tissue; C, polynuclear leucocytes; D, polynuclear leucocytes (spider cells) in the wall; D′, polynuclear leucocytes (spider cells) in the follicle. (Pappenheim staining.) $\frac{1}{12}$ obj. No. 4 eyepiece.

Note.—Most of the polynuclear leucocytes within the follicle have assumed their ordinary shape, with the exception of a few marked D′, whilst those in the dense connective tissue wall are spider-shaped, owing to their retention in that position during fixation.

other, evidently derived from the proliferation of the connective tissue cells which compose the wall. No contents of the old follicle remain, they having either been thrown off or destroyed by the polynuclear leucocytes (fig. 34).

(*b*) As the result of contraction of the newly formed fibrous tissue around the follicle the contents are compressed. As has already been seen,

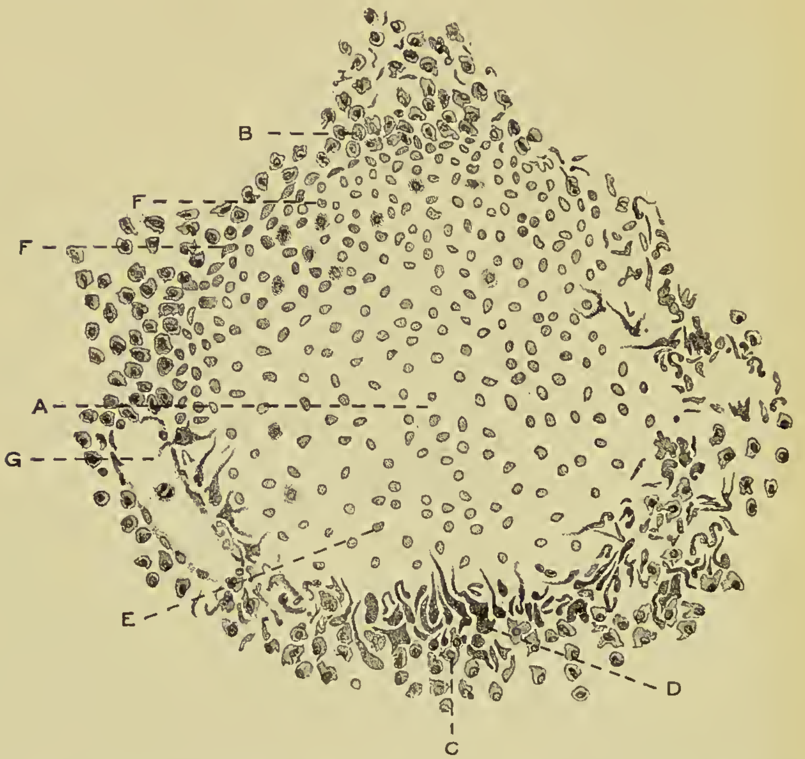

FIG. 35.—Early sepsis in a trachomatous follicle (A). B, Plasma cells; C, plasma cells degenerating; D, polynuclear leucocytes; E, contents of the follicle, much degenerated, in the region of polynuclear exudation; F, unchanged contents of the follicle; F[1], remains of the "radzone"; G, blood-vessel. (Pappenheim staining.) $\frac{1}{12}$ obj. No. 4 eyepiece.

directly between the follicle and the epithelium is a layer of plasma cells, which do not develop to any extent into fibrous tissue; the epithelium overlying the follicle becomes thinner, partly, no

doubt, by the friction and partly from atrophy produced by the prominent follicle beneath. As a result the follicle ruptures, its contents being partly extruded and partly removed by the polynuclear leucocytes which secondarily invade it on account of the sepsis which invariably follows, the conjunctival sac in these cases always containing pyogenic organisms.

(*c*) I have several sections which show the early changes produced by sepsis. The polynuclear leucocytes are found chiefly in the walls of the follicle, and do not seem to readily invade the follicle itself at first. The cells within the follicles, around the margin, show signs of degeneration, which is best seen when one side only of the follicle is attacked. Finally, the follicle becoming filled with polynuclear cells, ruptures through the surface, the cavity subsequently undergoing cicatrisation (fig. 35).

No doubt the beneficial effect of jequirity, and the effects of gonorrhœal ophthalmia on trachoma, are largely due to this cause, the polynuclear leucocytes attacking not only the disease in the follicle but the infiltration also.

(2) *Organisation of the Follicle.*—Although this method of resolution is given by some authorities, I have never been able to satisfy myself that it ever occurs without previous rupture, for in none of my sections can I find a definite fibrous or even partly fibrous nodule, such as would be produced by the organisation of a follicle.

Conclusions as to the Origin and Effects of the Disease on the Cells of the Follicle.—As we have already seen, trachoma is produced by direct infection. The actual cause of the disease has not yet been discovered, and although numbers of organisms have been described, none has yet been identified as pathogenic of the disease. Without doubt, whatever the cause of the disease, it has a very powerful action on the cells, for we have seen the amount of destruction it produces in the centre of the follicles, where, presumably, the disease is most active. As a result of the destruction of these cells hyalin material is formed, which may subsequently develop other changes (pl. iii., fig. 2).

In the follicles of follicular conjunctivitis we find great numbers of plasma cells, whereas in a definite trachomatous follicle they are practically absent.

Now, if plasma cells are derived from the endothelium with the lymphocytes, how is it that they do not appear in the follicles of trachoma? The answer to this question seems to me twofold. Firstly, plasma cells, to judge by their intensely basic staining reaction, are probably young cells, and very active proliferation of the endothelium is not taking place. Secondly, I have shown that plasma cells are not very resistant to toxins, and are easily broken up; hence, if formed, they would quickly disappear. Indeed, Whitfield has suggested that the presence of these cells is evidence of an attempt at the local immunity of the part.

It has been stated that follicular conjunctivitis and trachoma are identical diseases, and that the milder follicular conjunctivitis is simply the beginning of trachoma. This statement was made before the introduction of plasma stains, and I think anyone who has studied these two diseases by these methods would say that this is obviously incorrect. All the follicles in trachoma do not show the changes above described, many of them showing no change beyond that found in the so-called follicular conjunctivitis. This, I think, is due to the fact that they are not infected with trachoma, for if we take an analogous example, such as the cases in which tuberculosis affects the follicles, necrosis can be seen in some of the follicles which are side by side with perfectly healthy ones. The effect of the tubercle bacillus on the cells is very nearly like that of trachoma, causing destruction of the plasma cell at the most active site of the disease, with an increased formation outside the diseased area.

Similarly, in the early stages of tuberculosis of the lymphatic glands, there are often found follicles in the same gland which are not affected with the disease (pl. iv., fig. 4).

I take it, therefore, that the granules in trachoma are follicular formation plus trachomatous infection, the follicles being simply an effort on the part of the tissue to produce mononuclear cells, and becoming secondarily infected with trachoma.

PLATE IV.

FIG. 1.—Trachoma. Section through the bulbar conjunctiva and limbus, in a case of trachoma with severe pannus. showing a trachomatous follicle at the limbus. A, position where the limbus joins the cornea; B, necrotic area in centre of the follicle; C, well-formed plasma cells of the bulbar conjunctiva; D, degenerating plasma cells around the follicle; E, epithelioid cells within the follicle; F, blood-vessels within the follicle. (Pappenheim staining.) $\frac{1}{12}$ obj. No. 4 eyepiece.

FIG. 2.—An early deposit of tubercle in a lymphoid follicle showing necrosis of the plasma cells. A, Area of cellular necrosis; B, ring of degenerating plasma cells; C, well-formed plasma cells; D, endothelial phagocytic cell; E, blood-vessel. (Pappenheim staining). $\frac{1}{12}$ obj. No. 8 eyepiece.

PLATE 4

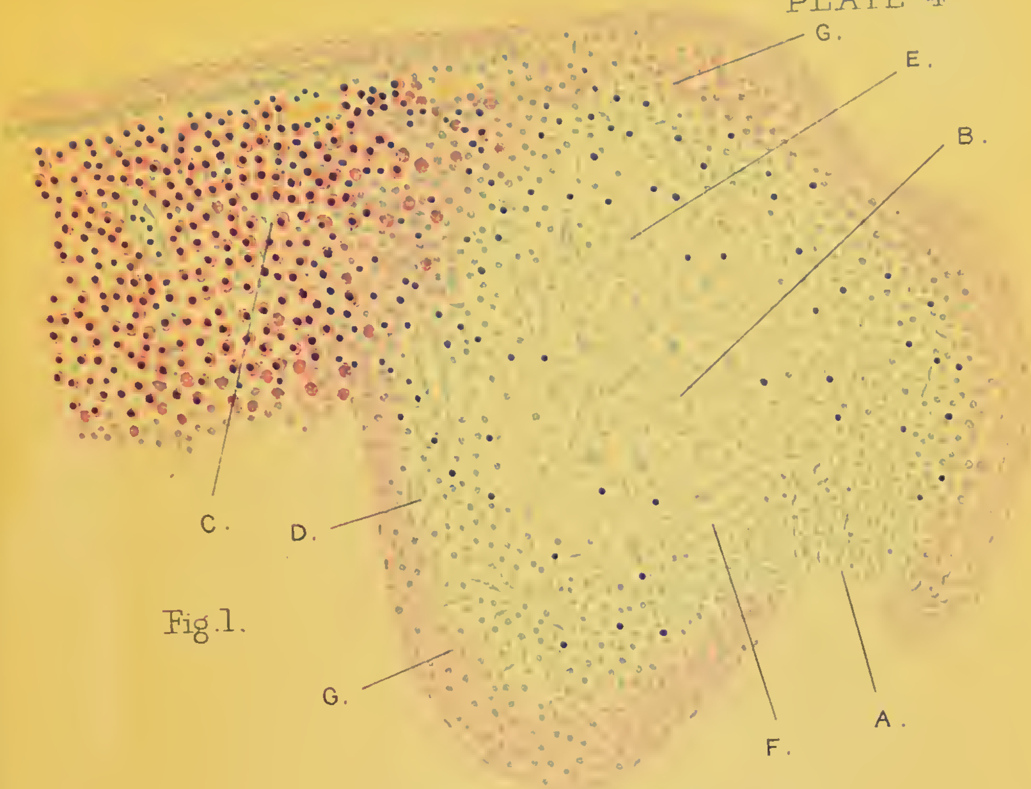

Fig. 1.

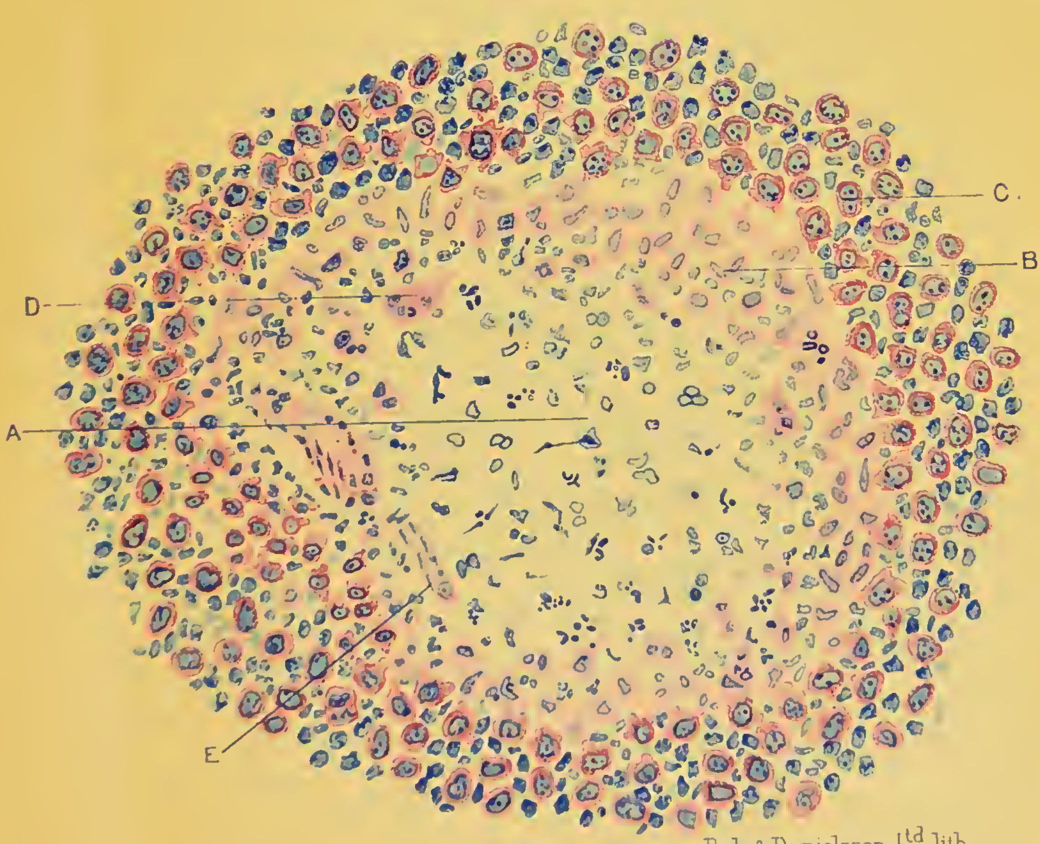

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Fig. 2.

Although, indeed, as a general rule a considerable number of them seem to be infected even in quite the early stages, as is evidenced by the cells beginning to show signs of degeneration and by plasma cells being absent, yet follicles can be found in trachomatous conjunctivitis which are packed with well formed plasma cells, and are evidently not infected with trachoma. These follicles may contain considerably more plasma cells than those of follicular conjunctivitis.

The Differential Diagnosis of Follicular Conjunctivitis and Trachoma.

Clinically, the differential diagnosis of trachoma and follicular conjunctivitis is made principally from the following facts :—

(1) The follicles in follicular conjunctivitis are found principally in the lower fornix, whilst those of trachoma are in the upper. Follicles also occur on the tarsus in trachoma.

(2) Scarring is absent in follicular conjunctivitis.

(3) Pannus is absent in follicular conjunctivitis.

(4) It has been said that trachoma is most common in adults, although I think that there is considerable doubt about this statement ; whereas follicular conjunctivitis occurs principally in children.

Microscopically.—(1) *Smear preparations* from the conjunctiva, obtained by gentle friction, contain an enormous number of plasma cells in trachoma ;

in follicular conjunctivitis, although the discharge often contains a certain number, they are not found to the same extent.

(2) *Sections.* — (*a*) *The epithelium* in follicular conjunctivitis, although showing extensive mucoid change, does not dip down into the tissue to the same extent, and there is not so much new gland formation.

(*b*) *The subepithelial tissue* in trachoma consists almost entirely of plasma cells; in follicular conjunctivitis, although they occur in large quantities near the follicles, they are not packed together beneath the epithelium as they are in trachoma.

(*c*) In trachoma there is an increase in the fibrous tissue, which often contains a large number of mast cells, and the connective tissue cells proliferate, the mononuclear exudation extending into the deep layer of the conjunctiva. In follicular conjunctivitis the deeper layers of the conjunctiva are unchanged. The follicle in trachoma contains practically no plasma cells, and in the centre the cells are undergoing necrosis and there are very few cells undergoing mitosis.

Epithelioid-like cells are absent from the follicles of follicular conjunctivitis, but are present in trachoma. The older follicles of trachoma contain considerable numbers of well-formed connective tissue cells, which are practically absent in follicular conjunctivitis. In sections from both diseases one usually finds follicles of varying age; it is there-

fore generally possible to make a differential diagnosis. But it must also be remembered that a trachomatous conjunctiva may have a healthy follicle, which may contain even a greater number of plasma cells than in follicular conjunctivitis. The most important point in determining the diagnosis is the necrosis of the cells, which in trachoma can not only be seen in the follicle, but in the infiltration. (See Stelwag's brawny œdema.) (Pl. iii., fig. 2.)

The Histology of the Bulbar Conjunctiva in Trachoma (pl. iv., fig. 1).

The epithelium shows some short papilla-like processes which dip down into the subconjunctival tissue. It is also somewhat thickened on the surface.

Subepithelial Tissue.—It is usually stated that the bulbar conjunctiva is unchanged in trachoma. This is not, strictly speaking, correct. I have had the opportunity of examining three cases of bulbar conjunctiva in trachoma removed by peritomy, in which there was considerable infiltration of the lids and well marked pannus. The subepithelial tissue showed a great increase in the number of plasma cells. Some of the plasma cells making up these masses can be seen forming chorioplaques, showing most beautifully their typical formation. A quantity

of new vessels with proliferating endothelium are also seen.

As the limbus is approached this layer is greatly increased in thickness and the plasma cells in the deeper layers show extensive degeneration.

At the limbus there are found a number of collections of lymphocytes and mononuclear leucocytes, surrounded by masses of plasma cells in every stage of degeneration. These masses of leucocytes degenerate into epithelioid-like cells towards the centre. There are no plasma cells in these masses, although the surrounding tissue consists practically of nothing else. In fact, the whole appearance is like that of the follicles seen in the lids, except that these follicles at the limbus are smaller in size, contain no darkly staining outer zone, and have a smaller number of plasma cells.

Conclusions as to the Changes at the Limbus.

There has been considerable discussion as to whether the condition of the limbus is a true infection with trachoma, or not.

I think from examining the above described sections that the answer is without doubt in the affirmative.

It is generally admitted that the bulbar conjunctiva is not affected with trachoma. No doubt as the result of the irritation produced by the friction of the granules over the surface, it becomes

filled with well-formed plasma cells showing that the disease is absent; but, as the limbus is approached, the tissue alters entirely. The plasma cells disintegrate and masses of mononuclear leucocytes make their appearance, whilst at the limbus we find plasma cells completely absent and the mononuclear cells in every stage of degeneration, forming a typical trachomatous follicle similar to that seen in the fornix.

Histology of Pannus.

I have only been fortunate enough to cut sections of one case of pannus in which the eye had been hardened in alcohol. Clinically the case was not of very great severity, the pannus covering about the upper third of the cornea and not very dense.

The epithelium over the surface of the cornea was slightly thickened and towards the lower margin of the pannus a break in the epithelium, evidently a small ulcer, could be seen.

Subconjunctival Tissue.—Beneath the epithelium there were a considerable number of new vessels surrounded by lymphocytes and plasma cells. In one situation these had formed a more or less rounded accumulation, somewhat resembling a modified follicle. Clinically I have seen cases of very thick fleshy pannus, in which, if sections of it had been made, I am sure that true follicular formation would have been found. Indeed, I think that

pannus is nothing more than the spread of the disease from the limbus to the cornea, modified by the dense nature of the tissue and the absence of blood vessels.

Histology of the various Forms of Trachoma.

Papillary Trachoma.

In this form of trachoma, the conjunctiva, when examined clinically, is seen to be covered with minute papillæ, like the pile on velvet. As a rule this condition is found in the early stages of trachoma and as it subsides the follicles make their appearance.

Histology (fig. 36).

The epithelium is thrown into folds by the swelling beneath, the surfaces in apposition showing mucoid change; in fact they form the so-called new glands.

The subepithelial tissue consists of an exudation of mononuclear leucocytes and plasma cells, the plasma cells being principally found directly beneath the epithelium, especially at the summit of the papillæ. Beneath the papillæ are found typical trachomatous follicles which are usually small, and whose existence is masked by the papillæ. There is comparatively little fibrous tissue, in fact the papillary condition seems to be characteristic of the early stage of the disease.

BRAWNY ŒDEMA (STELWAG).

(Pl. iv., figs. 2 and 37).

In this condition the upper palpebral conjunctiva is converted into a pale gelatinous-looking tissue; it is usually associated with much scarring and is

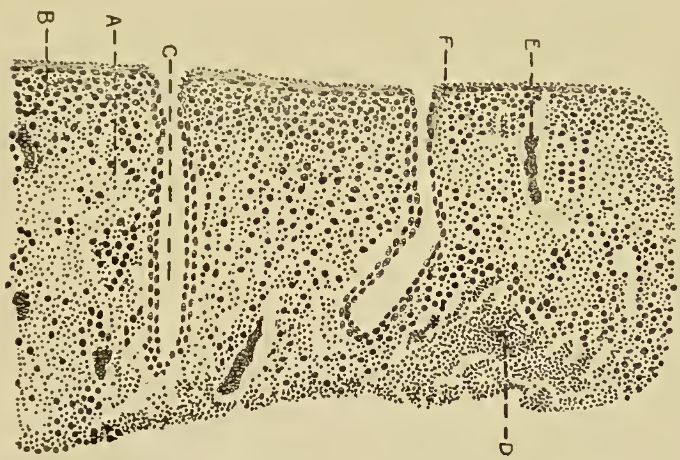

FIG. 36. — Papillary trachoma. A, Papilla; B, plasma cells situated principally beneath the epithelium; C, crypts between the papillæ, the epithelial cell lining of which is undergoing mucoid change; D, portion of a trachoma follicle lying beneath the papillæ, which clinically mask the presence of the follicle; E, blood-vessel in the papillæ; F, epithelium, which is thinner on the top of the papillæ than in the crypts. (Pappenheim staining.) $\frac{2}{3}$ obj. No. 4 eyepiece.

generally found in cases of trachoma of long standing. Microscopically, the condition is of considerable interest.

The epithelium is thickened and is often keratinised, and, unlike the other forms of trachoma, is not thrown into folds, but is smooth on the surface.

The subepithelial layer consists of infiltration much broken up by fibrous tissue, there being practically no follicular formations. The infiltration consists of a few mononuclear cells and a large number of plasma cells; these latter cells are found in all

FIG. 37.—Trachoma. Stelwag's brawny œdema. A, Epithelium which in many places has undergone keratinisation; B, infiltration which consists almost entirely of lymphocyte and plasma cells, most of which are undergoing degeneration (*see* pl. iii., fig. 2); C, fibrous tissue. (Stains: Logwood and Eosin.) $\frac{2}{3}$ obj. No. 4 eyepiece.

stages of degeneration, their cytoplasm being much broken up, but still taking the pyronine stain. When separated from the cells this material is found both free in the infiltration, and scattered through the fibrous tissue, constituting a form of hyalin degeneration. The newly-formed fibrous tissue

takes up the pyronine of Pappenheim's stain on that account. Sometimes this hyalin material goes on to secondary changes such as amyloid and calcareous degeneration.

Treatment.

Prophylaxis. — Trachoma being a contagious disease, and seeing the large percentage of cases whose sight, if not totally destroyed, is yet seriously impaired, the sufferers in consequence being often unable to carry on their occupation, it becomes a grave question whether this disease should not be made notifiable by law ; at any rate, in cases where large bodies of people are concerned, as, for instance, armies, factories, schools, &c. ; and, what is perhaps more important still, in the case of emigrants coming to this country, large numbers of whom are suffering from this disease, and, being refused admission to other countries, take refuge in ours. The great offenders in this respect, whom I have had a special opportunity of observing, both at the London and Moorfields Hospitals, are the Jewish emigrants from Poland, numbers of them arriving in England with trachoma, many of them being in the early stages of the disease, which in some instances was probably communicated to them on their way over.

In the case of school children it is especially urgent that some method of dealing with the

disease should be adopted, as the future livelihood of the child depends on its sight.

At present, nothing is done in this country to prevent the spread of the disease, with one notable exception in the case of the London District Pauper Schools (Metropolitan Asylums Board).

Owing to the protracted nature of the disease, general notification is no doubt almost impracticable at the present time; but in the case of Board Schools, where children are constantly brought in contact with this and other contagious ophthalmic diseases, some precautions should be taken to prevent their spread.

In the case of the Pauper Schools, homes are provided in the country, to which patients are sent, in which they are educated and at the same time treated for the disease.

It seems to me that the least that should be done in large towns is to provide separate schools for children suffering from ophthalmia, giving the parents the option of having their children treated at these institutions or at one of the general or special hospitals. It cannot be too strongly emphasised that children suffering from trachoma, or other contagious ophthalmia, ought on no account to be allowed to mix with healthy children and so spread the disease broadcast.

Arrangement of Sanatoria.

It is not proposed to discuss in detail the arrangement of suitable buildings for children suffering from ophthalmia. Usually such buildings are arranged on the separate block system; that is to say, there is a central administration building with rooms for medical officers, matron, &c., surrounded by cottages, in each of which six to twelve patients suffering from the same disease are placed, each group of cottages containing the same disease being provided with a nurse who superintends and carries out the treatment. Central schools are provided in which all the children meet, but all have their own separate desks from which they are not allowed to move. A room adjoining the schoolroom is provided, in which the children can be treated during school hours. An infirmary and isolation building are also provided for use in the event of a child becoming ill or suffering from a general infectious disease. The whole of these buildings are placed in large grounds, preferably in the country, in which the children out of school hours can play.

The greatest care is exercised in providing separate towels, &c., for each patient. Ordinary baths and washing basins are dispensed with and warm water douches are used instead, as less likely to give rise to infection. All linen, &c.,

is sterilised in a large laundry adjacent to the institution.

When once a patient is infected with trachoma or any other form of contagious ophthalmia, he should be isolated as much as possible; that is to say, a child should not attend ordinary school; the greatest possible care should be taken of his linen, especially that with which his eyes are liable to come in contact, such as pillows, handkerchiefs, towels, &c. These should be placed in strong carbolic and washed separately from the other clothes. The patient should not sleep in the same room or bed as other people, and separate sponges, flannels, &c., should be provided for him to wash with.

When one eye only is affected the patient should be warned against infecting the other. He should be told to sleep on the affected side to prevent the discharge running over the nose and infecting the other eye. If an eye bath be used, the patient should be specially warned not to use it for the sound eye, and to take the greatest care with regard to handkerchiefs, &c.

In the case of nurses and medical men, they should take every precaution against the infection of their own eyes in the course of treatment. Especially is this so when expression operations are performed, when protective spectacles should be worn.

The Local Treatment.—Probably for no disease

have so many methods of treatment been advanced, which goes far to prove that the methods adopted are not very satisfactory; and, indeed, until late years the treatment of this disease had practically not improved since the days of Celsus. Until the cause is discovered there is little hope of obtaining a specific cure.

At the present time the treatment consists in:—

(1) Getting rid of the follicles by operative measures; and (2) producing phagocytosis by *chemicals*, such as caustics; *e.g.*, copper sulphate; by *inoculation* with specific organisms or ferments; *e.g.*, gonococcus, jequirity; by *ultra violet radiation; e.g.*, X-rays, radium, &c.

It is quite impossible to describe in detail all the different forms and methods of applying the various agents used. Therefore only those which are commonly in use, together with the methods which I have found most satisfactory, will be described.

No. 1. *Removal of the Follicle.*

Expression.—There can be no doubt that this form of treatment is most satisfactory in the case of follicular enlargements. Unfortunately we have no means at the present time of distinguishing between infected and uninfected follicles. It acts, no doubt, first by getting rid of the central foci of the disease in the follicles; and, secondly, by

the cavities from which they are evacuated becoming septic, and the mechanical irritation producing an increased polynuclear phagocytosis into the tissues.

The operation may be performed under cocaine and adrenalin, a little solid cocaine being rubbed into the area to be expressed. In severe cases, in which both eyes are affected, and in small children, a general anæsthetic may be necessary.

Although a number of instruments are in use, perhaps the best, and certainly the least painful, is Graddy's forceps. In the case of the upper lid it is everted, one blade of the forceps being passed into the fornix, the other being placed over the upper surface of the everted lid. A gentle, steady pressure is applied and the lid drawn out between the blades. In this way as much of the conjunctiva is gone over as is necessary.

In the case of one or two follicles they can be picked up with the ordinary fine dissecting forceps and expressed. But when on the tarsus the follicles are best enucleated by a spud. A little orthoform subsequently rubbed in relieves the pain experienced by the patient when the effect of the cocaine has worn off. Subsequently the lids may be treated by one of the various methods to be described later on.

Brushing.—The lids are brushed over with a hard tooth-brush, the brush causing laceration of the epithelium and extrusion of the follicles. It

is a comparatively clumsy method compared with expression, causing a greater loss of tissue and necessitating a general anæsthetic for its use.

Scarification.—Scarification by metal brushes is also used, but there is the same objection to it.

Friction.—Friction has been used since the days of Celsus, when it was performed with a fig-leaf. Now it is usually applied by a brush or with one of the caustics to be described.

No. 2. *Methods of Producing Phagocytosis.*

(*a*) *Chemical.—Solid copper sulphate* is perhaps most frequently used for this purpose, as with it a certain amount of friction can be applied, and it stains the conjunctiva less than other caustics, although, as Stephenson has pointed out, copper oxide becomes deposited to a slight extent. (*Trans. Ophth. Soc. U.K.*, 1903). It is best used in the form of a smooth pencil, the points which show most changes being especially picked out. It should be used daily in the more severe cases. The pain after its use generally lasts from three to four hours, and may be alleviated by using cocaine at the time, adding orthoform to the copper stick, and bathing the eyelids directly afterwards with iced water.

Fluid.—Hydrarg. perchlor., 1-50, in glycerine and water, applied by rubbing into the lids with a wool mop, is perhaps not so satisfactory as the former drug, but is useful after expression.

Silver nitrate has the great drawback that, after prolonged use, the silver is reduced and stains the conjunctiva (argyrosis). This can be partly averted by using protargol. This drug is especially valuable when there is much discharge, and in cases where injection of the lids remains after the disappearance of the granules.

The conjunctiva when affected with argyrosis is microscopically of interest, as it shows to some extent the depth to which the chemical penetrates. It is seen on section that the silver is deposited especially in the basement membrane of the epithelium, but it is also found in the subepithelial tissue, in the endothelial cells both of the blood-vessels and of the follicles especially picking out the cement material between these cells. That it is found within the endothelial cells is, no doubt, due to the phagocytic properties of these cells.

The great disadvantages of treatment by caustics are :—

(1) They produce an excessive amount of scar tissue.

(2) They cause considerable pain.

(3) They have practically no effect on the pannus, which is the most important objection of all, as vision depends on that clearing up.

(*b*) *Inoculation.*—It has been found in some cases of trachoma which became infected with gonorrheal ophthalmia that the former disease disappeared. Intentional infections have been made in several

cases, but the method has been given up as too dangerous, corneal perforation having occasionally resulted.

Jequirity was first used in Brazil. It was prepared as an infusion from the seeds of the *Abrus præcatorius.* Its action, as De Wecker pointed out, is due to the presence of an unorganised ferment which belongs to much the same order as the snake poisons. When inoculated into the conjunctival sac it produces a muco-purulent conjunctivitis of a somewhat varying severity, which cannot be regulated and is therefore dangerous.

Lately the toxin has been isolated from the ferment and is called Jequirol ; this toxin is standardised in three separate strengths and produces a similar reaction to that caused by the ferment when applied to the conjunctival sac, but which can be regulated to some extent. It is usually applied by painting it over the surface of the lids two or three times in half an hour and then waiting for the reaction to come on.

If this toxin be injected into animals in gradually increasing doses an antitoxin is found in the serum. This is also seen in patients treated by this method, who after a time become immune to its action. The clearing effect on the pannus is often very marked. The antitoxin is produced in the cells of the conjunctiva, for if a piece of conjunctiva from a jequirity ophthalmia be transplanted into the peritoneal cavity of an animal, the animal is rendered immune to the action of the ferment.

(*c*) *Ultra-Violet Radiation.—X-rays.*—Whilst watching some years ago the clinical and histological changes which take place in rodent ulcer and lupus of the eyelid under X-ray treatment, and finding no seriously injurious effect on the globe or other structures, it occurred to me that it might be possible to apply this form of tissue stimulation to other diseases of the eye, more especially to trachoma and corneal opacities. With that idea, a case of severe bilateral trachoma was, in April, 1902, admitted into King's College Hospital for treatment.

After twenty-four exposures to the X-rays the disease disappeared, and the patient remains well up to the present date.

In order to obtain the best possible result from any form of treatment, it is essential to know not only the pathology of the disease which is being treated, but also the action on both normal and diseased tissues of the agents used.

Therefore, before passing to the method of carrying out this treatment, something must be said as to the action of the X-rays on the tissues generally, and on the eye in particular.

It has lately been shown that these rays are in all probability ultra-violet rays which have been polarised. There seems to be no doubt that the rays are not all of the same wave length, as differing amounts of vacuum in the Crookes' tube produce rays that have differing powers of penetration, and

also varying effects on the tissue; that is to say, high vacuum tubes have more penetration power with less effect on the tissues, whilst low vacuum tubes have less penetration with more effect on the tissues.

When healthy living tissues are exposed to their action a superficial inflammation is produced, which does not seem to affect much beyond the main superficial vessels. The capillaries of the area exposed become enormously dilated and there is a large exudation of leucocytes. This inflammation may result in anything from a mild erythema to the sloughing of the area exposed, according to the amount of exposure.

It seems to be brought about in exactly the same way as by other forms of stimuli—chemical, mechanical, electrical, or thermal—and the first three degrees of burns, as described by Dupuytren, compare admirably with the various degrees of so-called dermatitis produced by X-rays.

But the application of X-rays differs from all these other forms of stimuli in being painless; this may be due to the fact that the stimulus is very slight, although prolonged, or it may be that the nerve endings in the skin cannot appreciate it. The inflammation produced differs also in that it is more persistent than in an ordinary burn, and the smaller vessels of the part become permanently dilated after prolonged exposure. The changes do not make themselves apparent till from one to three

weeks after exposure, and therefore care must be taken not to over-expose the part before reaction fully sets in. These changes are intensified and more rapidly brought about by the simultaneous application of irritants, such as copper sulphate, &c.; and, conversely, if a part is already irritated or inflamed, its reaction to X-rays is much greater. This will account for the enormous leucocytosis seen around the epithelial cells in rodent ulcer cured by this method, and the same thing is seen to occur around the follicles in trachoma, the rodent cells and trachomatous follicles acting as irritants.

To come next to the effects of X-rays on the eye, taking instances of prolonged exposure.

In a case of rodent ulcer in which, owing to the contraction causing ectropion of the lower lid, the globe was exposed for eight months to the action of X-rays, ten minutes' exposure four times a week being given, no ill-effect on the media, iris or fundus could be detected, the vision remaining $\frac{6}{9}$ throughout the treatment.

In another case of rodent ulcer involving the margin of the lid, which was exposed for two and a half months, averaging three times a week for eight minutes, no effect on the globe was noted, although it was examined frequently, the vision remaining $\frac{6}{6}$ throughout the treatment: this was two years ago, and the eye still remains healthy. Two other cases similar to these have been examined and no change found.

In all the above cases an acute conjunctivitis was produced, and this is also seen among men employed in X-ray work, but it is easily prevented in them by the use of lead-glass spectacles. The conjunctivitis was very acute in some instances, and was often of the purulent variety. Nearly all the eyelashes fell out owing to an inflammatory change round the hair follicles, but came again readily after cessation of the treatment. With the amount of exposure required to cure trachoma, however, neither of these effects need be produced.

Fuch and Kreidel, in 1896, showed that there was no bleaching of the visual purple by X-rays; possibly this might have been expected, seeing that the photographic action of X-rays is dependent on the fluorescence they produce. Since the tubes of that date were probably not so powerful as those now in use, I have recently made somewhat similar experiments on rabbits and frogs.

In the case of rabbits, the animals were kept in the dark for four hours, and then killed with $CHCl_3$, and both eyes were enucleated in a dark room under a ruby light. One eye was then exposed to the action of the X-rays for half an hour (8 amp., 3-inch spark-gap) at a distance of six inches, the eye being covered by a black cloth so as to screen off the light rays. Both eyes were put for three to five minutes in iced saline solution to inhibit the bleaching of the visual purple. The anterior halves of both eyes were then removed

and evaginated on the finger tip, and examined by an electric arc lamp, such as is used in the Finsen treatment of lupus: there was no bleaching of the visual purple found in either eye. A small scratch was made on the surface of the retina of the eye that had not been exposed to the X-rays, so that by bleaching of the visual purple, through the injury, a comparison of colour could be made; the visual purple took about one minute to disappear under the influence of the light.

In the case of frogs, the eyes were similarly enucleated and exposed. The entrance of the optic nerve was then buttonholed and the anterior half of the globe removed, the retina being withdrawn from the vitreous, mounted in saline solution on a slide without a cover-glass, and examined with the microscope. No bleaching of the visual purple was seen, but it disappeared slowly under the influence of the light in from twenty minutes to half an hour.

In the X-rays we have a method of setting up a leucocytosis with the absolute minimum of destruction to epithelial and other tissues; and, further, we have a means of producing an inflammation, varying from a very slight leucocytosis to an actual gangrene of the part, which, with due care and experience, we have under almost perfect control.

Not knowing the organism which causes trachoma (if such organism exist), we cannot say whether the irritants which are used in its treat-

ment, or X-rays, have any effect on it. But we have in X-rays a method of producing leucocytosis in any degree, from that corresponding to a mild application of perchloride of mercury up to that induced by jequirity ; and, further, this leucocytosis is much more prolonged than in any method formerly adopted, and the destruction of tissue is not nearly so great.

Although granules disappear very rapidly under X-rays, operative methods, which have the additional advantage of removing the diseased tissue, may be preferable to some extent, except that the patient has to undergo an operation ; but such operations can be followed by X-rays to complete the work, in preference to one of the other irritants now in use. But operation should never follow X-ray treatment without considerable interval, owing to the great reaction which is set up.

In the first case, the method adopted was to cover the whole face, with the exception of the affected eye, with a metal mask. Since then I have discarded the mask altogether, as now the patient is never exposed sufficiently to get any reaction in the skin. The upper lid is everted, and the lower lid pushed up so as to cover as much of the cornea as possible, but in bad cases of pannus the cornea is left exposed ; I have never had any trouble with the globe following X-ray treatment.

The operator's hands are protected with bismuth ointment and cotton gloves, a separate pair of

which is kept for each case, or a Reid's[1] or Collins' clamp may be used.

The patient is seated about nine inches from the anode, with a moderately soft tube and a current of six amp. Four minutes' exposure is given for four to six successive days, depending on the case. If there be much injection or the case be an acute one, four is generally sufficient. A week's rest is then given, and if no reaction be set up the patient is exposed three to five times a week until there is a slight increase in the photophobia, which shows that the patient is beginning to react. About this time the granules begin disappearing from the lids. Exposures are carried out until they disappear. When the granules have disappeared all treatment must be stopped, as it requires some weeks for the infiltration set up by the X-rays to settle down, and it is difficult to tell whether the disease is absolutely eradicated, as the lid remains injected for some time after treatment has ceased.

The final result to the lid is most satisfactory. Instead of the white, puckered conjunctiva produced by other methods, a supple, non-contracted, non-scarred conjunctiva, with no obliteration of the fornices, unless they are already gone before treatment, is gained, similar to the soft supple scar in the skin produced by this form of treatment in

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[1] *British Medical Journal*, July, 1903.

rodent ulcer, as compared with the dense cicatrix of excision.

As regards the effect on pannus, it often clears with great rapidity, especially if recent, and it is a common thing for patients to say that they see more clearly from almost the first exposures. But even dense corneal opacity will often clear considerably, and in one case of extensive destruction and cicatrisation of the cornea, following thirty years of trachoma, in which at the commencement of treatment the patient could only see shadows, in two months she could count fingers three feet away.

Another peculiar point is the amount of exposure required by different patients. Sometimes the granules begin to disappear from almost the first exposure ; others require eight or ten or more exposures before showing signs of reaction.

As regards the cases suitable for treatment, the most satisfactory are the subacute and chronic cases, and of course the earlier they seek treatment the more rapid and satisfactory the result. These patients will stand more frequent exposures than any others ; acute diffuse infiltrations, with thickening of the lids and much photophobia, require more careful exposure, extending over a much longer period. Old-standing cases in which the lid trouble has almost disappeared, but in which there is much opacity of the cornea, will often improve considerably under exposures at long

intervals after the first reaction which should be mild.

The chief advantages of this treatment are :—

(1) There is considerably less deformity of the lid after treatment.

(2) It is practically painless treatment.

(3) Pannus clears more thoroughly.

The chief disadvantages are :—

(1) All patients do not react well to X-rays.

(2) It is difficult to say when to cease treatment. This was especially marked in the first few cases treated, some of which recurred, but cleared up under further treatment.

In the periods of rest between the exposures to the X-rays the application of copper is very useful, but care must be taken in applying it, as the reaction produced by the copper is increased by the previous application of the X-rays.

Since introducing this treatment, cases treated successfully have been reported by S. Stephenson (35 cases), Bettermieux (4 cases), E. T. Collins (40 cases), Pardo (2 cases), Cassidy and Rayner (4 cases), Geyser (18 cases), and myself (27 cases). W. S. Newcomet, J. P. Krall, and I. F. Schamberg have also reported cases. I know also of several other successful cases unrecorded. The maximum number of exposures given was in a case of my own, namely, 81, with two others over 50. Mr. E. T. Collins reports a case which had over 40. The minimum number of exposures in which the

case was discharged as cured and did not return was six in one case and nine in another.

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Radium.—In two cases in which I have tried radium-bromide, although the pannus and granules improved, marginal ulceration, with falling out of the lashes, was produced, so that the treatment had to be abandoned. It is, however, probable that with better methods of application it will prove to be of value in the treatment of trachoma.

High Frequency Currents.—I have treated several cases with the high frequency current without any success. The application was somewhat painful.

With regard to determining when any form of

treatment should cease, it is practically impossible to say when trachoma is cured. Certainly, all the granules should have disappeared from the lid, injection should be absent, and, most important of all, since it may carry contagion, the discharge should have ceased. This latter is best determined by bandaging the eye at night-time. Even when all these conditions are satisfied, a patient occasionally returns with a recurrence of the disease.

Phlyctenula.

Although this name (meaning "a little bladder") is not, strictly speaking, accurate, since the exudation, at any rate at first, consists of cells, it seems to be rather better than some of the other names, such as conjunctivitis eczematosa, or herpes conjunctiva, which are incorrect as to their pathological significance and give a wrong impression.

Clinically, in its simplest form, a phlyctenule is a small red eminence about the size of a millet-seed, usually seen in the ocular conjunctiva in the region of the limbus with a leash of dilated vessels leading up to it. As a rule, the epithelium on the surface of the eminence gives way, with the extrusion of the contents and the formation of a greyish-looking ulcer which rapidly heals. Occasionally these nodules disappear without the formation of an ulcer. Almost invariably the disease is preceded by some other form of con-

junctivitis, it being very rare to find a case in which there has not been some slight discharge beforehand, if the history be carefully enquired into.

The *position* of the phlyctenule is by no means limited to the limbus, although without doubt that is the most common situation of the lesion. It is found in other parts of the bulbar conjunctiva, and, according to H. Herbert (*Ophth. Review*, 1898), it occurs on the palpebral conjunctiva.

This statement I have had the opportunity of verifying in a child suffering from a muco-purulent conjunctivitis, due to the *Staphylococcus pyogenes albus*, accompanied by pustules on the face, due to the discharge from the eye. On the outer side of the limbus was a typical phlyctenule. On everting the upper lid there were three or four follicular-like enlargements on the palpebral conjunctiva covering the tarsus, one of which was ulcerating. There were no other follicles in the upper or lower fornices, or in the other eye. A piece of this tissue, containing two of the phlyctenules, was removed for examination. The other phlyctenules disappeared in one week under protargol. (Microscopic examination given below.)

Since seeing this case I have observed several other cases with phlyctenules on the palpebral conjunctiva of the upper lid, and not infrequently have found another phlyctenule on the bulbar conjunctiva in the position where the eyelid lay

in contact with the globe, the one having no doubt produced the other by direct infection.

Finally, phlyctenules may start in or spread to the cornea from the limbus, and, when lasting for some time, become vascularised by the budding out of the endothelium of the vessels from that region.

The *number* of phlyctenules varies considerably. In some cases there are only one or two, in others they may be extremely numerous, the conjunctiva in the neighbourhood of the limbus being covered with very small nodules which do not usually break down into ulcers, but resolve. In cases in which the discharge from the eye runs down over the face numerous pustules are formed in the skin from direct infection.

The patients are usually children, although not invariably so, and are as a rule run down in health. It is stated that these children are always tuberculous, and it is supposed by some authorities that these lesions are of a tubercular nature, but since the surroundings which give rise to both diseases are the same, this theory is of but little value, especially as the pathological changes do not bear it out.

Histology.—I have had the opportunity of examining eight cases microscopically, which showed most of the stages of the disease.

The tissue was fixed in alcohol, cut in paraffin, and stained with logwood and eosin, Pappenheim's and Gram's methods, and for tubercle with carbol-fuchsin and methylene blue.

A Commencing Phlyctenule (fig. 38).—The epithelium over the surface of the phlyctenule is intact. The exudation in the early stages consists largely of mononuclear leucocytes, which may be situated either in the superficial or in the deep layers of the subepithelial tissue of the conjunctiva. If in the

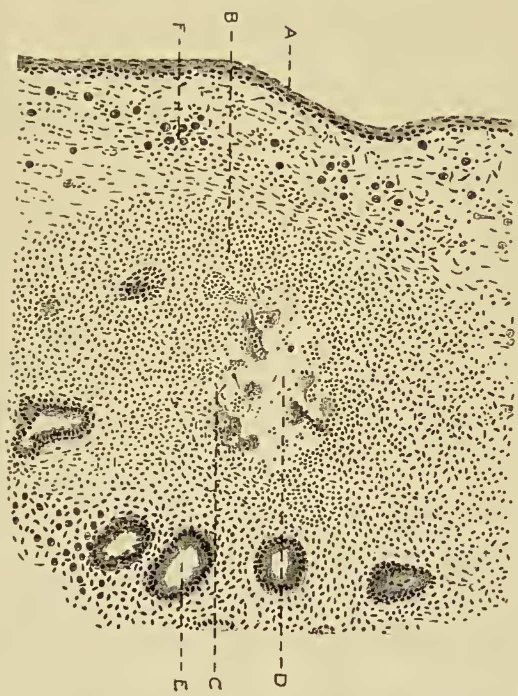

FIG. 38.—Early deep phlyctenule from the upper lid. A, Epithelium ; B, mononuclear exudation ; C, polynuclear leucocytes ; D, necrosis in the centre of the phlyctenule ; E, Henle's glands ; F, plasma cells. $\frac{1}{8}$ obj. No. 4 eyepiece. Long tube.

superficial layer it is much more diffuse and constitutes the efflorescence so often seen at the limbus in these cases. If in the deeper layer it is much more localised and forms the typical nodule belonging to this disease.

In the centre of this mass of mononuclear cells

is found an area in which the cells are undergoing necrosis, and in this region there are generally found some polynuclear leucocytes. All round this exudation can be found a slight increase in the plasma cells, but whenever these cells appear in the exudation they degenerate. The blood-vessels in

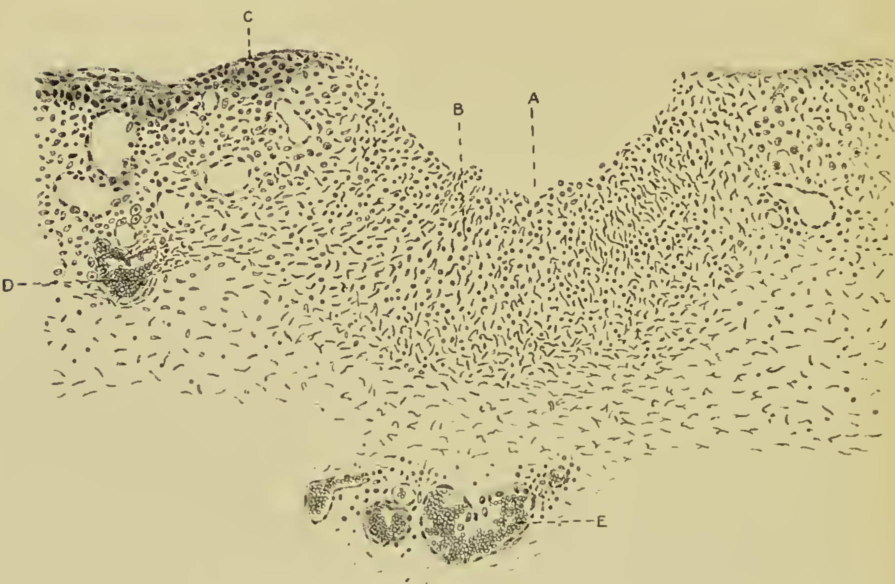

FIG. 39.—Ruptured phlyctenule. A, Surface of the ulcer; B, polynuclear leucocytosis; C, epithelium infiltrated with polynuclear leucocytes; D, vessel showing diapedesis (polynuclear leucocytes); E, vessel in deeper part of conjunctiva, surrounded by mononuclear cells. (Pappenheim's staining.) $\frac{1}{6}$ obj. No. 4 eyepiece.

the neighbourhood are dilated and the endothelium is proliferating. In the lid case previously described, the tissue removed contained a typical phlyctenule in this stage, and also contained one just after rupture. A phlyctenule in the early stage may end in (1) rupture, (2) resolution.

A Ruptured Phlyctenule (fig. 39).—The exudation, making its way along the path of least resistance, ruptures through the epithelium. Although the number of polynuclear leucocytes have increased before rupture takes place their number is enormously multiplied directly it does so, the epithelium in the neighbourhood as well as the walls of the lately evacuated phlyctenule being infiltrated with these cells, which are principally of the spider cell type. Around the old phlyctenule the vessels are found to be greatly dilated, and the endothelium proliferating; the exudation around these vessels varies, sometimes consisting of mononuclear cells and sometimes of polynuclear leucocytes; there are also a number of vessels of new formation. The plasma cells are slightly increased in number and mast cells are beginning to make their appearance.

A Healing Phlyctenule.—The epithelium is spreading over the surface of the ulcer produced by the rupture of the phlyctenule. The subepithelial tissue consists of practically nothing but dilated and newly formed vessels with proliferating endothelium. The number of new vessels which the tissue contains is extraordinary, every field of the $\frac{1}{12}$ containing five or six minute new vessels. Scattered amongst these new vessels are found large numbers of mast cells. In places there are also found patches of mononuclear and polynuclear exudation.

A Resolving Phlyctenule differs only from a

healing phlyctenule in that comparatively few polynuclear leucocytes are found, the exudation being broken up by the proliferating endothelium of the new blood-vessels, which, if anything, are more numerous than in the healing phlyctenule. Large numbers of mast cells are present (fig. 40).

A Healed Phlyctenule.—Occasionally the epithelium is found dipping down into the subepithelial

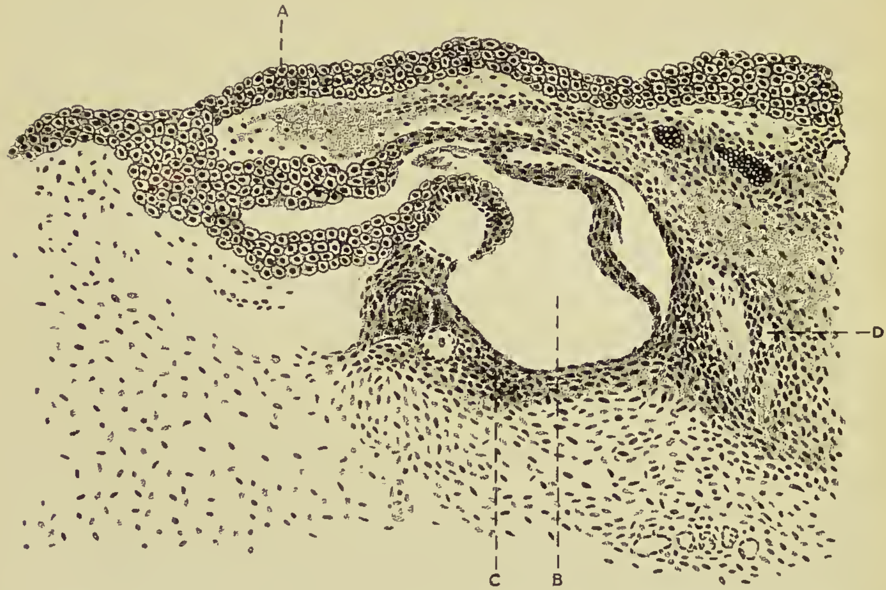

FIG. 40. — Phlyctenule immediately after healing. A, Surface epithelium ; B, cyst produced by downgrowth of epithelium ; C, part of cyst wall, lined by single layer of epithelium only; D, dilated blood-vessel. (Pappenheim's staining.) ⅔ obj. No. 2 eyepiece.

tissue at the site of the healed ulcer. In the subepithelial tissue the proliferating endothelium and the new vessels have to a great extent disappeared, and the surrounding conjunctiva is regaining its normal condition (fig. 40).

Bacteriology.—In the eight cases previously mentioned the discharge contained in five cases the Koch-Weeks bacillus, and in two the *Staphylococcus pyogenes albus*, one case being a mixed infection of both. Two of the cases were members of families of three, all of whom attended the hospital with Koch-Weeks conjunctivitis.

Th. Axenfeld (*Trans. Heidelberg Soc.*, 1897) examined the discharge from a number of cases, and came to the conclusion that, although the staphylococcus is the principal organism found, he did not think it specific to the disease. Albt. Michel (*Annales d'Oculist*, October, 1899) comes to the same conclusion.

Axenfeld, Müller, Bach and Neumann were unable to find organisms within unruptured phlyctenulæ. I have myself failed to find any definite organisms in either unruptured or ruptured phlyctenulæ in histological sections. This obviously does not prove, however, that the disease is not due to organisms introduced by ectogenic infection, as any organisms in such a situation would be very difficult to detect. Bach was also unable to produce phlyctenulæ by rubbing cultures of staphylococcus into the healthy human conjunctiva.

Conclusions.—This disease, like tuberculosis, is essentially associated with low vitality in the patient and diminished resistance to bacterial invasion. Hence it is only natural that these

diseases should often be found in the same subject.

The discharge in cases of phlyctenular conjunctivitis runs over the face and produces suppurating points in the skin. We know that if the staphylococcus is rubbed into the skin it will produce similar suppuration. But Leber, like Bach, has been unable to reproduce the disease by inoculating the healthy conjunctiva with the pus from these points. This, I think, may probably be accounted for by the healthy condition of the persons experimented on, just in the same way that crops of boils constantly recur in the skin in patients who are out of health through reinfection from the discharge, but cease to form directly the health is re-established.

With regard to the histology, although in the early stages the exudation is chiefly mononuclear, it becomes polynuclear before rupture takes place, a point which is almost positive evidence of the presence of pyogenic organisms. The occurrence of the mononuclear cells, I think, can be accounted for by the special tendency of the conjunctiva to form mononuclear cells, as has been shown when treating of the lymphoid tissue of the conjunctiva.

The most frequent seat of phlyctenulæ is the limbus, a point at which the conjunctiva is attached firmly to and supported by the globe, so that the lid, passing constantly over the surface, is more likely to rub the organism in. Although the

corneal conjunctiva is equally subject to friction from the lid, the entrance of organisms is probably hindered to some extent by Bowman's membrane, although phlyctenular ulcers do occur here also.

Another factor, undoubtedly, is the absence of lymphoid tissue, for we find that phlyctenulæ only occur where none exists.

The whole course and histology of a phlyctenule correspond very closely to that of a boil on the skin, to which, I think, it is exactly comparable, with the exception that it occurs in a thin membrane in which rupture takes place very early. In the cornea, where the tissues are thicker, definite macroscopic abscesses are occasionally found.

When the disease starts in or spreads to the cornea the ulcer which is produced often persists for a considerable time, the endothelium of the vessels which bud out from the limbus vascularising its base. The long duration of a phlyctenular ulcer in the cornea, compared with that of one at the limbus, is very marked, which is, I think, accounted for very largely by the non-vascular condition of the cornea, for we have seen that a healing phlyctenule at the limbus consists practically of new vessels and proliferating endothelium.

The comparative absence of the plasma cell in this disease is of considerable interest. We have seen that this cell does not make its appearance to any extent during acute inflammatory processes, but

in tuberculosis around the foci of the disease it is present in enormous numbers. In other words, the non-appearance of the plasma cell in phlyctenulæ is indicative of an acute inflammatory process, and therefore not due to tubercle, which produces plasma cells in immense numbers. In the healing stage plasma cells are not present to any extent, and we have already seen in trachoma, &c., that the presence of the plasma cell is an indication of the local immunity. So, again, in phlyctenulæ their non-appearance is associated with the fact that phlyctenule after phlyctenule can recur about the same region.

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Vernal Catarrh.

Arlt first described this disease in 1846, but Horner first pointed out its main characteristics.

In this disease the tarsus becomes covered with broad, flat papillæ, which have been compared to

cobblestones. Adherent to the surface is a thin layer of milky mucoid secretion, which becomes more marked if the conjunctiva be subjected to the least irritation. If the condition has lasted for some time the limbus becomes greatly thickened

FIG. 41.—A papilla from a case of vernal catarrh, showing the distribution of the eosinophiles in the epithelium and subepithelial tissue. A, Epithelium ; B, eosinophiles ; C, fibrous tissue ; D, break in the epithelium. Many of the eosinophiles are found in the epithelium. (Staining: Leishman.) $\frac{2}{3}$ obj. No. 8 eyepiece.

and nodular. The symptoms of photophobia and lachrymation generally appear during hot weather.

Histology. The condition is one of enormous papillary overgrowth of the conjunctiva.

The *epithelium* is thickened over the surface of the papillæ, and in the folds dips down into the underlying tissue. As a rule these processes show comparatively little mucoid change.

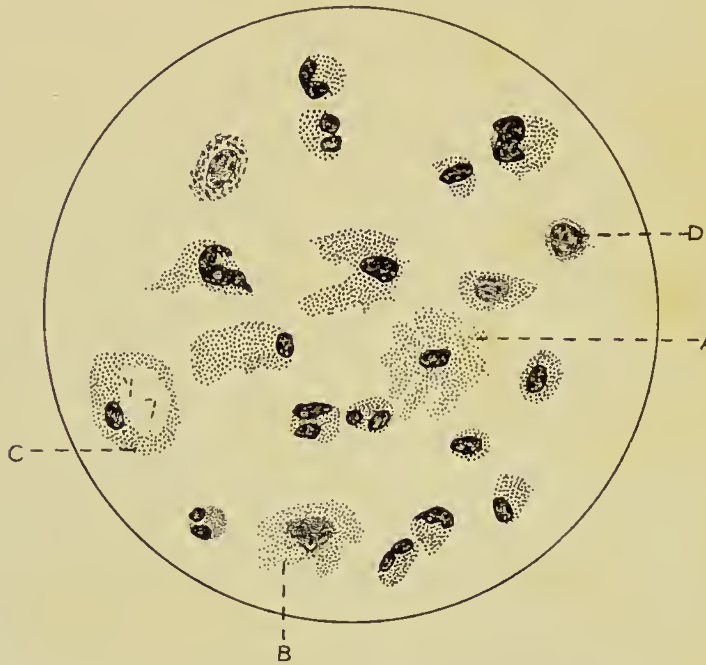

FIG. 42.—Vernal catarrh. A typical microscope field of the discharge from a case of spring catarrh. A, An eosinophile which has ruptured scattering its granules; B, hypochromatosis; C, phagocytosis; D, lymphocyte.

Subconjunctival Tissue.—(Fig. 41) The papillæ on the tarsal conjunctiva are very hard and consist of a quantity of dense connective tissue. It has been pointed out by Herbert (British Medical Association Meeting, 1903) that in addition to the ordinary connective tissue cells there are a quantity of

eosinophile cells, and that these cells are present in the discharge—a point which he considers diagnostic. I have examined six cases histologically, and can confirm this point in every way. The eosinophiles, both polymorphonuclear and mononuclear, are found in immense numbers in the discharge, whole fields of the $\frac{1}{12}$ often containing

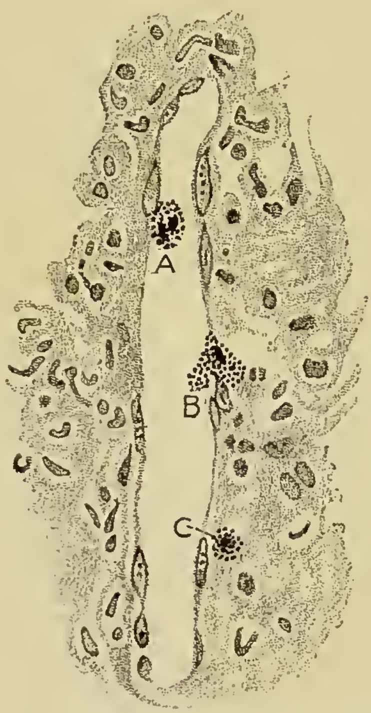

FIG. 43.—Vernal catarrh, showing the diapedesis of the eosinophiles. A, Eosinophile within a vessel; B, diapedesis; C, eosinophile outside the vessel. (Differential staining: Logwood and eosin).

no other cells. The granules from the cells, which are often ruptured, being scattered through the specimen, are best demonstrated by staining with Leishmann's eosin-methylene-blue compound (fig. 42).

In the tissue they are far less in proportion to the other leucocytes, their appearance in such large quantities in the discharge being due to their greater power of amæboid movement. They are situated principally in the small vessels lying

FIG. 44.—Vernal catarrh, showing the necrosis in the plasma cells. A, Plasma cell showing fragmentation of its cytoplasm ; B, hyaline material free in the tissue. (Pappenheim staining.)

beneath the epithelium, and can be seen coming through the vessel walls, being derived from the blood. (Fig. 43) I could find no evidence of proliferation of these cells in the tissue. According to Herbert they make their way through breaks in the epithelium. Although this is so, all my sections

show them actually in the epithelium making their way through it.

In addition to these cells there are considerable numbers of plasma cells, most of which show marked necrosis, evidently due to the presence of some powerful toxin (fig. 44).

Summary of the Changes which Occur in the Subepithelial Tissue of the Conjunctiva as the Result of Inflammation, as shown by their Histology.

In studying inflammation in the conjunctiva we are dealing with a tissue which is very responsive to the slightest stimulus, and the cells of which are normally undergoing proliferation in the superficial layers. It is moist and warm, well supplied with blood, nerves and lymphatics — all factors which assist in rapid tissue change.

The Cells.—The character of the cells found in the exudation depends on the character and degree of virulence of the toxin introduced into the conjunctiva; if this be extreme, as in the case of the pyogenic micro-organisms, there follows a response, not only locally in the tissue of the conjunctiva, but from other tissues of the body, such as the bone-marrow, with the resultant exudation into the conjunctiva of polynuclear leucocytes,[1] brought by the

[1] The polynuclear leucocytes are mostly neutrophile, but in some forms of exudation, such as that occurring in vernal catarrh, the eosinophile cells may predominate.

blood stream from other tissues to the inflamed conjunctiva, as is seen also in the early stages of a wound, or in acute muco-purulent ophthalmia. When the toxin is not so virulent, especially when the subepithelial tissue is directly affected, as in the early stages of a phlyctenule, the local response on the part of the tissue is the production of mononuclear leucocytes. These cells are probably derived from the rapid proliferation of the perithelium and endothelium of the blood-vessels, lymphatics, glands, &c., which in the conjunctiva produce these cells with enormous rapidity.

The conjunctiva is always receiving a certain amount of irritation and, therefore, is producing mononuclear cells, the only period at which these cells are absent from the tissue being the fœtal stage of existence, when naturally no irritation occurs. Now, when the degree of irritation is increased, as in the case of atropine irritation or in the later stages of Koch-Week's conjunctivitis, there is an increased call on the tissue for the production of mononuclear cells, followed by the formation of follicles. This follicular formation also occurs in children, without any special cause of irritation, at the age when the lymphoid tissue is unusually active, and is then known as follicular conjunctivitis. The follicles are either small and discrete or large and containing a number of other follicles (which I have called endo-follicles); the latter variety are identical with lymphatic glands,

which, like the follicles, may be of new formation. Subsequently these follicles, like the lymphatic glands, can become the seat of disease, such as tubercle, trachoma, &c., and the cells undergo secondary degenerative changes, such as hyalin, amyloid, &c.

In all inflammatory changes of any duration the plasma cell is produced, its presence in large numbers being significant that the disease is chronic or of a non-virulent type, such as diplobacillary conjunctivitis. Its origin is closely allied to that of the mononuclear leucocyte, its structure and staining reaction being very similar to those of the large mononuclear leucocyte; in fact, the plasma cell is possibly nothing more than a slightly altered large mononuclear leucocyte, and is probably a young cell, because of its basic staining reaction. It may be either directly derived from the mononuclear cells or differentiated in the process of their formation from the perithelium and endothelium. It seems to me impossible that the plasma cell can be, as is stated by Unna, derived from the fixed connective tisssue cell, for reasons already given.

The great importance of these cells in conjunctival disease is that, if they are formed, they show the situations in which disease is present by disintegrating in that area; and, conversely, by their presence they show the local immunity of the area in which they are found, for if we look at sections from ophthalmia neonatorum of some

duration, we find the deeper tissue packed with plasma cells, whilst directly beneath the epithelium, which is known to contain the organisms producing the disease, plasma cells are absent. Between these two areas, one consisting almost wholly of plasma cells and the other having practically none, we find plasma cells in every stage of disintegration. In the follicles of the so-called follicular conjunctivitis (normal lymphoid tissue), they are present in large numbers, whilst in the trachomatous follicle they are broken up. Again, in the bulbar conjunctiva of trachoma, which is admittedly not affected with the disease, they are present in large numbers, but as the limbus is approached they decrease and disintegrate, and in the diseased follicle at the limbus they are absent.

Again, in wounds of the conjunctiva they appear in twelve hours, simultaneously with the comparative cessation of exudation of polynuclear leucocytes; that is to say, the wound has become at that time locally immune from any organism it may contain, if not acutely septic.

Around a phlyctenule very few plasma cells are found; in connection with which fact we note that phlyctenulæ constantly recur in the same situation.

The endothelial and perithelial cells, as well as being the probable origin of the mononuclear leucocytes and plasma cells, are strongly phagocytic, for it is seen that they take up the particles of silver oxide in argyrosis, and also polynuclear

and mononuclear leucocytes and plasma cells, which within these cells undergo a process of digestion. They are so numerous in resolving follicles that it would seem that they may account largely for the disappearance of the exudation after the cause of the inflammation is removed.

No doubt also the disappearance of the exudation is assisted by the return of a certain proportion of its cells into the blood stream and the lymphatic vessels; but the whole subject of resolution and organisation is too vast to be treated of here, and belongs rather to the realm of general pathology than to that of the special pathology of the conjunctiva.

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* These two references do not apply to the plasma cell of Unna.

INDEX.

12

PAGE